Asymmetric Rhodium Catalysed Additions to Activated Imines – New Approaches to α-Chiral Amines

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Abstract

This Thesis details the development of a series of rhodium catalysed asymmetric additions to activated aldimines to give enantioenriched protected secondary amines. A particular focus has been the choice of activating group to allow deprotection of the protected amines under mild conditions, which would tolerate a wide substrate scope.

Initially methyl addition to give enantioenriched arylethanamines was studied, using diphenylphosphinoyl imines, dimethylzinc as the methyl source with rhodium catalysis in the presence of a bidentate phosphine ligand. Reduction of the starting material was identified as side reaction with a Meerwein-Verley-Ponndorf type mechanism for the reduction being proposed. Addition of the imine to the reaction mixture *via* a syringe pump was found to minimise this by-product. The imine scope was tested with yields ranging from 34-73% and enantiomeric excesses from 75-93%.

Subsequently, aryl additions were concentrated on using aryl boroxines and boronic acids to give enantioenriched diarylmethylamine products. *Bis*-sulfamyl aldimines were identified as an overlooked substrate class for asymmetric aryl additions, which gave addition products that could be converted to free amines using mild basic aqueous conditions. The rhodium catalysed aryl boroxine addition using a chiral diene ligand was optimised after which a study into the reaction's scope was carried out. Yields ranged from 37-76% with diastereomeric ratios of 91:9->99:1 and enantiomeric excesses of 90->99%. Unfortunately, the unwanted *meso*-diastereoisomer could not be removed, leading to a lowering of enantiomeric excess after deprotection, nevertheless the free diarylmethylamine were isolated in yields of 31-99% and enantiomeric excesses of 82-97%.

Leading on from this work, a novel class of *N*-sulfamyl aldimines were developed which could be deprotected under the same mild conditions, and would avoid the problem of the undesired *meso*-diastereoisomer. A scalable synthesis of these substrates was developed. However, aryl addition proved more problematic with imine hydrolysis being a major side reaction. Eventually a set of conditions were settled on and the scope investigated briefly. The yields were found to depend on the electronic character of the substrates and the ligand employed.

Finally, a brief investigation into the iridium catalysed reductive coupling of these activated aldimines and alkynes to give allylic amines was carried out. However, useful conversions were not achieved, with imine and alkyne hydrogenation being competing reactions.

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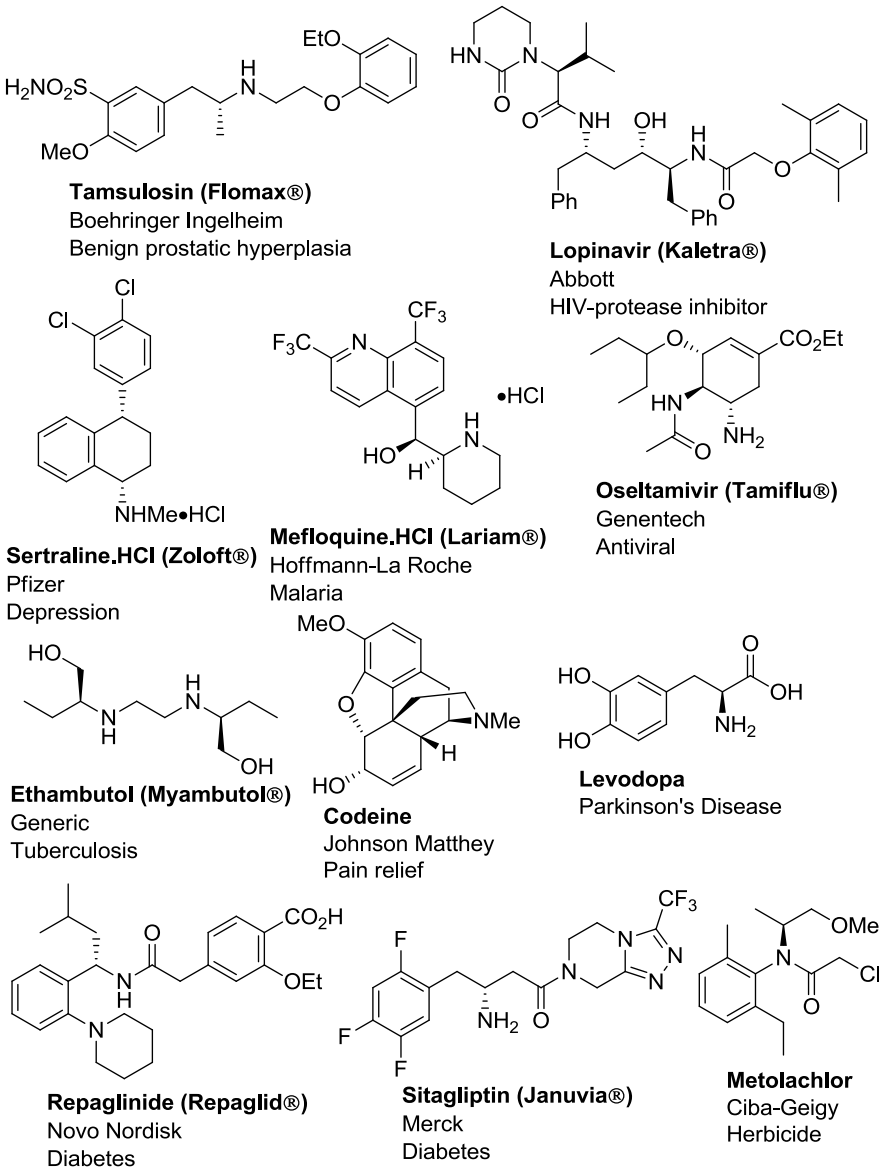
Abbreviations

app.	Apparent
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1-Binaphthol
BIPHEP	2,2'-Bis(diphenylphosphino)-1,1'-biphenyl
CBS	Corey-Bakshi-Shibata
coe	Cyclooctene
CSI	Chlorosulfonyl isocyanate
dec.	Decomposed
DPP	*N*-Diphenylphosphinoyl
dppb	1,4-Bis(diphenylphosphino)butane
dppbenz	1,2-*Bis*(diphenylphosphino)benzene
dppf	1,1'-Bis(diphenylphosphino)ferrocene
eV	Electron volt
FGI	Functional group interconversion
HMDS	Hexamethyldisilazane
m-CPBA	*meta*-Chloroperbenzoic acid
M.S.	Molecular sieves
MVP	Meerwein-Varley-Ponndorf
n.d.	Not determined
Ns	4-Nitrobenzenesulfonyl
Pet. ether	Petroleum ether
PG	Protecting group
PMP	*p*-Methoxyphenyl
psi	Pound per square inch
quant.	Quantitative
QUINAP	1-(2-Diphenylphosphino-1-naphthyl)isoquinoline
RAMP	(*R*)-1-Amino-2-(methoxymethyl)pyrrolidine
SAMP	(*S*)-1-Amino-2-(methoxymethyl)pyrrolidine
sat.	Saturated
TFE	Trifluoroethanol
Tol	Tolyl

Chapter 1 Introduction

1.1 Uses of α-Chiral Amines

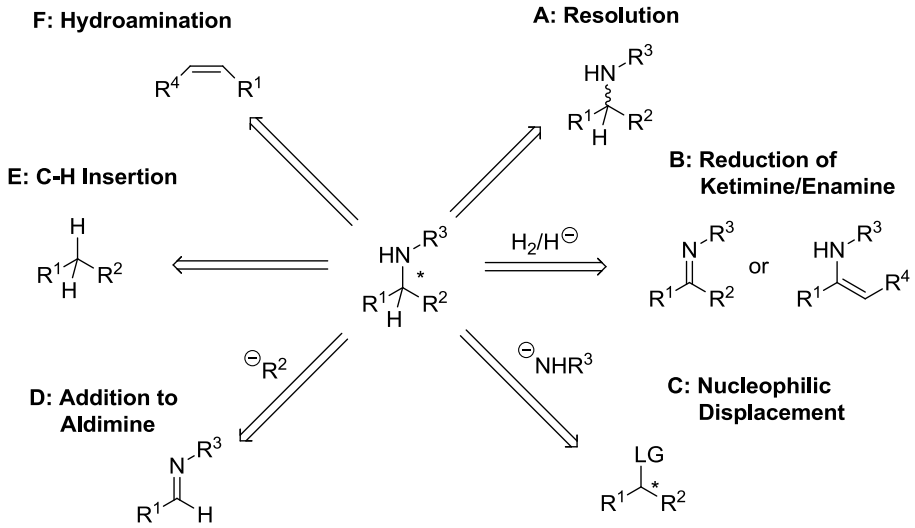
α-Chiral amines are ubiquitous chemical motifs occurring in pharmaceutical and agrochemical targets,[1] and used in the synthesis of enantioenriched compounds as chiral ligands, chiral auxiliaries and chiral bases.[2] This class of compounds is of interest in the areas of synthetic methodology, natural product synthesis, bioorganic and medicinal chemistry.[3] Scheme 1 shows a range of pharmaceutical and agrochemical active species containing optically active amines.



Scheme 1

1.1.1 Routes to α-Chiral Amines

The efficient synthesis of α-chiral amines has been a significant goal for both academic and industrial research groups and is a current active area of research efforts.



Scheme 2

Various routes to secondary α-chiral amines are shown in Scheme 2 above, these include:

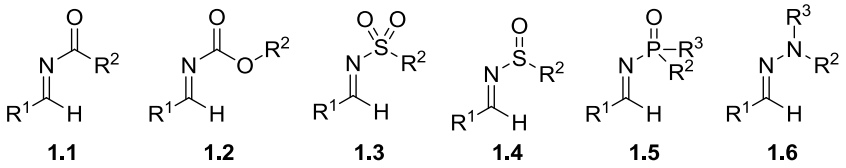
- Chemical or enzymatic resolution of a racemic amine (Route **A**).[4]
- Reduction of a ketimine or its enamine tautomer (Route **B**).[5]
- Nucleophilic displacement of a suitable leaving group (Route **C**), for example an azide or an activated alcohol (Mitsunobu reaction).
- Carbon-carbon bond formation between an aldimine, oxime or hydrazine and nucleophile (Route **D**).[6,7]
- C-H activation of a methylene unit (Route **E**).[8]
- Hydroamination of an olefin (Route **F**).

The research in this Thesis will focus on nucleophilic additions to aldimines (Route **D**), although other areas will be discussed.

1.2 Activated Aldimines

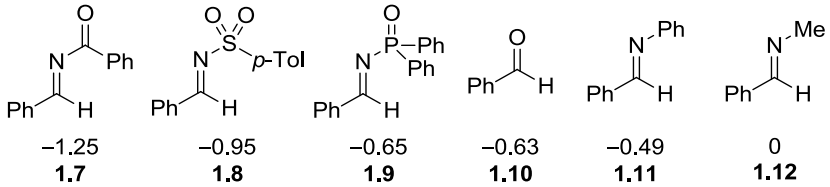
Imines are inherently less electrophilic than the aldehydes or ketones from which they are derived due to nitrogen's decreased electronegativity and as a result research in this area has lagged behind additions to aldehydes.[9] The electrophilicity of the imine can be increased by substituting the nitrogen with an activating, electron withdrawing group. Examples of such

activating groups are shown in Scheme 3. Forming oximes and iminium ions are other strategies for increasing reactivity; however, these will not be discussed in this Thesis.



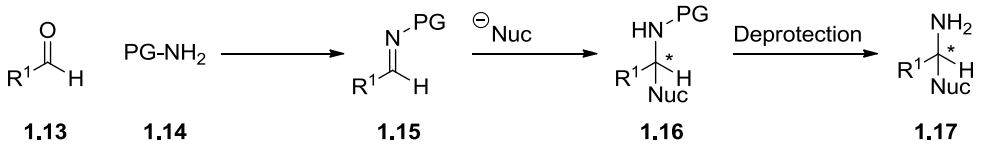
Scheme 3

The LUMO energies (in eV) of various activated imines and benzaldehyde **1.10** for comparison, relative to *N*-methyl imine **1.12**, are shown below in Scheme 4.[10,1] Alkyl and aryl substituted imines **1.12** and **1.11** are both less electrophilic than benzaldehyde. However, addition of electron-withdrawing groups such as tosyl **1.8**, diphenylphosphinoyl **1.9** and benzoyl **1.7** create increasing electrophilic species. The lower energy LUMO and increased electrophilicity of the azomethine carbon makes transition metal catalysed nucleophilic additions possible to these activated imines.



Scheme 4

Other issues encountered when working with imines are polymerisation, hydrolysis and enamine tautomerisation. Polymerisation is prevented by adding a substituent to the nitrogen atom. The stability of the imine is dependent on the substituent on the azomethine carbon, aromatic groups lead to much more stable imines than alkyl groups, which more readily decompose. However, this problem has been worked around in some cases by forming the imines *in situ* from a sulfinate adduct (see Sections 2.2 and 3.2). Imines with α-hydrogens are prone to deprotonation resulting in tautomerisation to the enamine form; for these reasons most research in this area has been carried out on aryl aldimines.



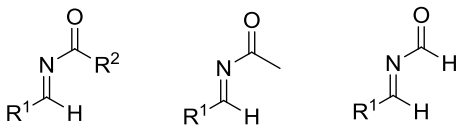
Scheme 5

Imines **1.15** are accessed from aldehyde precursors **1.13** typically by condensation with the appropriate amine **1.14** (Scheme 5). Nucleophilic addition gives a chiral protected amine **1.16**. The amine **1.14** is ideally inexpensive and readily available. Finally, the activating/protecting group must be easily removed from the resultant protected amine **1.16** to give the free chiral amine **1.17**.

Strategies for making enantioenriched amines fall into two groups. The first of these is addition to imines bearing chiral auxiliaries incorporated (asymmetric diastereoselective synthesis). The second of these is external chiral ligand controlled addition to an achiral imine (asymmetric enantioselective synthesis); the ligand may be present in stoichiometric or ideally catalytic quantities. As already discussed, it is necessary to add an activating substituent to the nitrogen atom; by having this as a chirally pure auxiliary this allows the possibility of diastereofacial selectivity when the nucleophile is added. No extra steps will be added to the synthesis provided the optically pure amine precursor is readily available in stoichiometric quantities; ideally, both enantiomers will be available. Non-racemic imines derived from enantiopure aldehydes and addition of chiral organometallic reagents fall outside the scope of this Thesis. Separation of the diastereoisomers prior to deprotection may give very good optical purities compared to resolution of enantiomers after asymmetric catalysis.[3]

External chiral ligands can be used alone or in conjunction with a transition metal catalyst. In both cases, the presence of the ligand creates a pair of diastereomeric transition states; the favoured, lower energy transition state will lead to the enantioenriched product. Catalysis with enantiopure ligands is the most efficient approach to enantioenrichment, with the enantiopure ligand only required in catalytic quantities.

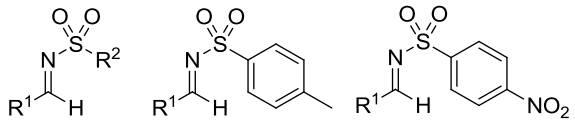
A short review of the most frequently used activating and protecting groups (both achiral and enantiopure) will follow. The availability of the amine precursor **1.14**, the reactivity of the activated imine and the removal of the activating group from the addition product **1.16** will be considered.



1.1 **1.18** **1.19**

Scheme 6

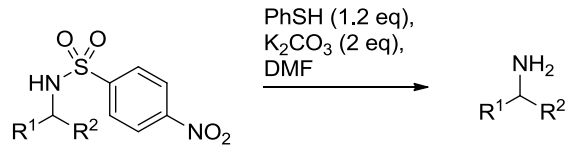
N-acylimines **1.1** (Scheme 6) are the most reactive of these activated imines,[11] however, this high reactivity is detrimental to catalytic asymmetric strategies as there can be significant uncatalysed background reactions.[12] Both **1.18** and **1.19** are synthesised *in situ* from their sulfinate adducts (see Scheme 22, Section 2.2.3). Some acylamines can be troublesome to deprotect needing forcing acidic conditions, addition products from *N*-formyl imine **1.19** can be deprotected using mildly acidic conditions.[13]



1.3 **1.20** **1.21**

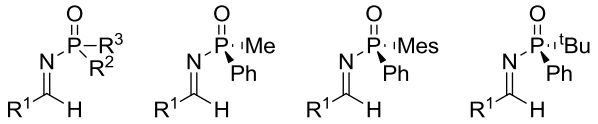
Scheme 7

N-Sulfonylimines **1.3** (Scheme 7) are one of the most commonly used activated aldimines. They are less reactive than *N*-acylimines however; they have the advantage of long-term stability. *N*-Tosylimines **1.20** are the most frequently cited *N*-sulfonylimines. Condensation of the readily available *p*-toluenesulfonamide and an arylaldehyde gives **1.20**; other synthesis routes are discussed in Section 3.4.2. The stability of the subsequent sulfonamide product can be a problem; to deprotect the tosyl group requires harsh conditions for example dissolving metal reduction or strong acids. An alternative is the nosyl group **1.21**, which can be removed by treatment with a thiol and base (Scheme 8).[14,15]



1.22 **1.23**

Scheme 8

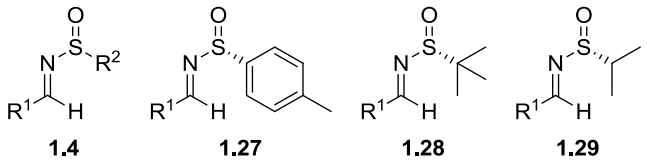


1.5 **1.24** **1.25** **1.26**

Scheme 9

N-Phosphinoylimines **1.5** (Scheme 9) are less reactive than *N*-sulfonylimines **1.3** and are also stable enough to be isolated and stored.[12] *P,P*-Diphenyl- and *P,P*-diethoxy- are the most common substituents.[16,17] They can be made by the condensation of *P,P*-diphenyl phosphinamide with arylaldehyde or by other methods discussed in Section 2.4.4. The resulting

phosphinamides are easily deprotected using mild acidic conditions. Recently a series of enantiopure *N*-phosphinoylimines imines have been developed **1.24**,[18] **1.25**[19] and **1.26**[20] amongst others.[21,22] See Section 2.4.4 for a further discussion of *N*-diphenylphosphinoylimines.



1.4 **1.27** **1.28** **1.29**

Scheme 10

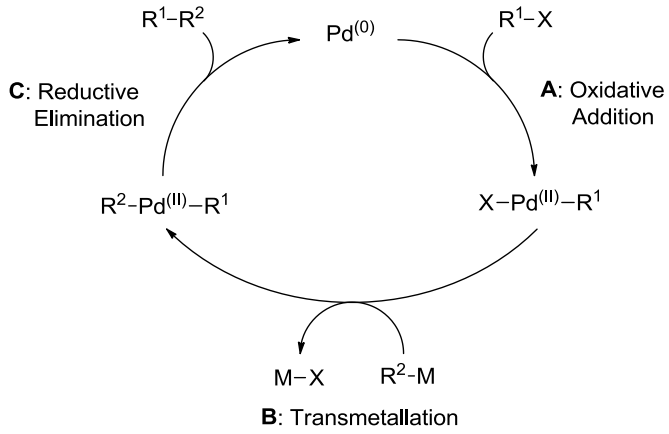
N-Sulfinylimines **1.4** (Scheme 10) are stable with both alkyl and aryl substituents from the aldehyde and undergo diastereoselective additions which, if the substrates are non-racemic, can lead to enantioenriched products. *N*-*p*-Toluenesulfinyl imines **1.27**,[23,24] *N*-*tert*-butyl imines **1.28**[25] and *iso*-propylimines **1.29**[26,27] have been developed. Imine **1.28** is the most widely used, with the required chiral amine being commercially available as both enantiomers. The resulting sulfinamides are deprotected using mild acidic conditions.

Further specific examples of enantioenriched amine synthesis will be reviewed at the beginning of the following chapters. This Thesis will discuss the asymmetric synthesis of arylethanamines (Chapter 2), diarylmethylamines (Chapters 3 and 4) and briefly, 1-aryl-2-propenylamines (Chapter 5).

1.3 Rhodium Catalysed Carbon-Carbon Bond Formation

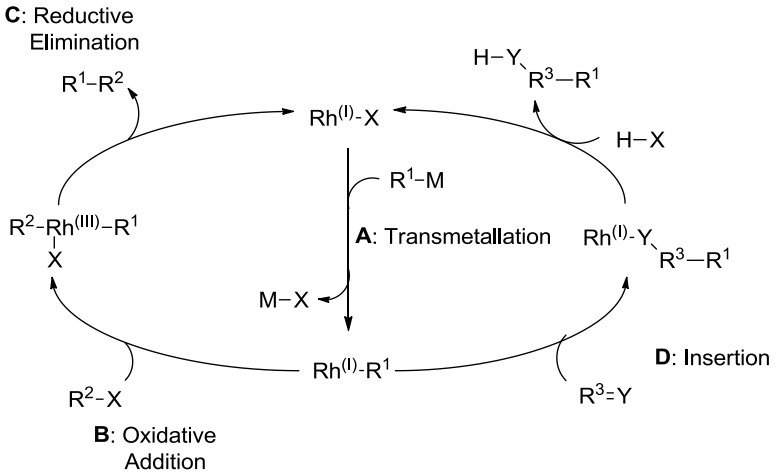
Another area that should be reviewed herein as it forms a major part of this Thesis is the use of rhodium to catalyse the formation of carbon-carbon bonds. The formation of carbon-carbon bonds using transition metal catalysis has been a major development in modern organic chemistry. Palladium has dominated this field of transition metal catalysis, with key cross-coupling reactions such as Suzuki-Miyaura,[28] Mirozoki-Heck[29] and Stille couplings.[30] However, rhodium catalysis has been a growing area recently as its use allows for alternative reactivity not possible with palladium. As well as its novel and often complimentary reactivity, another advantage of the use of rhodium is the reactions often withstand or require the presence of water which can possibly be used as a co-solvent.[31]

To understand the differences in their reactivity the catalytic cycles of palladium and rhodium must be compared. In a palladium cross-coupling catalytic cycle, the oxidation state of palladium shuttles between (0) and (II), with transmetallation only occurring at (II) oxidation level (Scheme 11).



Scheme 11

Rhodium, on the other hand, typically enters the catalytic cycle at an oxidation state of (I) allowing for transmetallation to occur as the first stage without the need for an oxidative addition (Scheme 12). Oxidative addition to give a $Rh^{(III)}$ species can then occur (left hand cycle, Scheme 12), followed by reductive elimination to give the equivalent product to the palladium cycle but with the step order reversed. Alternatively (right hand cycle, Scheme 12), an unsaturated bond can insert into the organo-rhodium complex to give addition of R^1-H across an unsaturated bond.[31] It is this mode of reactivity that is taken advantage of in this Thesis and that this review will focus on.

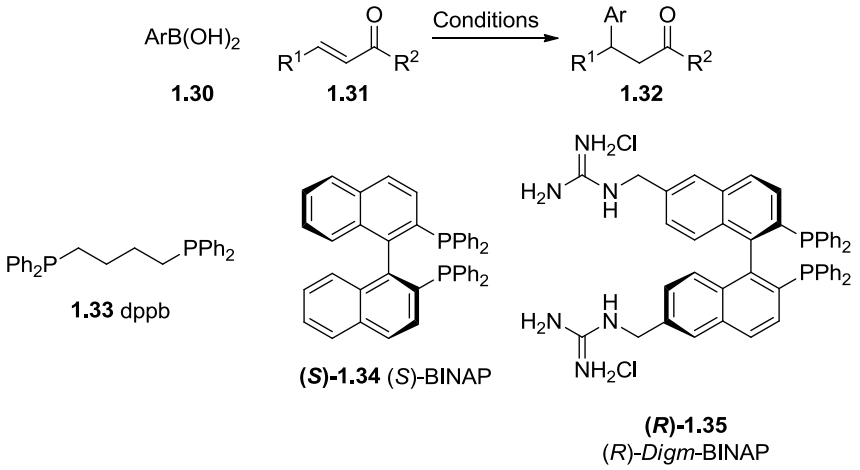


Scheme 12

Conjugate additions of organometallics to alkenes bearing electron-withdrawing groups have become a key reaction for rhodium catalysed carbon-carbon bond formation. Although excellent systems using alkylzinc compounds with copper asymmetric catalysis have been developed, there has been little success with aryl addition with this metal combination. Using rhodium catalysis 1,4-arylations of α,β-unsaturated carbonyl compounds have been made possible.[32]

In 1997, Miyaura *et al.* reported the first rhodium catalysed 1,4-additions of aryl- and alkenyl boronic acids to α,β-unsaturated ketones (Entry 1, Table 1).[33] An asymmetric reaction using (*S*)-BINAP **(*S*)-1.34** as a ligand soon followed in a collaboration between Miyaura and Hayashi using both linear and cyclic enones as substrates (Entry 2).[34] Amengual and co-workers have used a BINAP derived ligand **(*R*)-1.35** to give good enantiomeric excesses (Entry 3).[35]

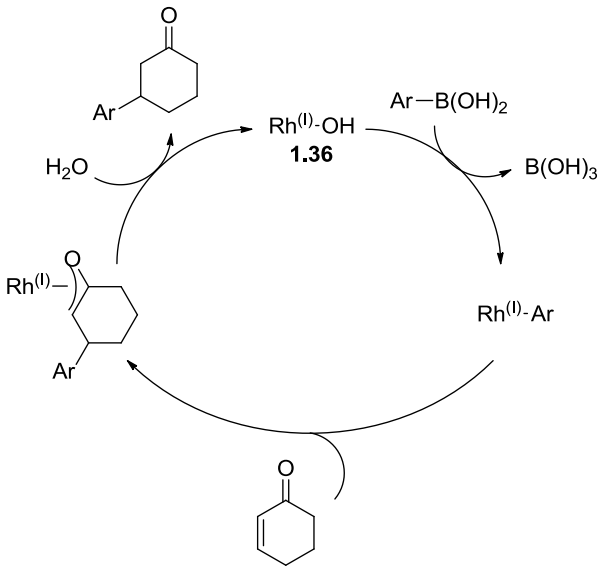
Table 1



Entry	Conditions	**1.32** [%]	*ee* [%]
1	$ArB(OH)_2$ (2 eq), $Rh(acac)(CO)_2$ (3 mol/%), **1.33** (3 mol/%), MeOH:H_2O 6:1, 50 °C, 16 h	84-99 6 examples[33]	-
2	$ArB(OH)_2$ (1.4-5 eq), $Rh(acac)(C_2H_4)_2$ (3 mol/%), **(*S*)-1.34** (3 mol/%), dioxane:H_2O 10:1, 100 °C, 5 h	51->99 9 examples	92-99 (*S*)[34]
3	$ArB(OH)_2$ (2.5 eq), $Rh(acac)(C_2H_4)_2$ (1 mol/%), **(*R*)-1.35** (1.2 mol/%), Na_2CO_3 (2 eq), ethylene glycol, 100 °C	44-100	81-98[35]

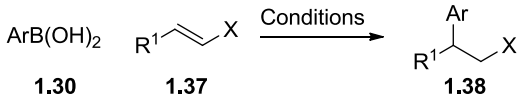
The mechanism of these conjugate additions is shown in Scheme 13, using cyclohexenone as an example substrate. The mechanism was probed by the group of Hayashi using ^{31}P NMR spectroscopy to study the coordinated phosphine ligands of the species present, with

hydroxyrhodium species **1.36** found to be the catalytic species.[36] Other unsaturated systems that have been studied in the rhodium catalysed aryl boronic acid addition are α,β-unsaturated esters,[37] α,β-unsaturated amides,[38] α,β-unsaturated phosphonates[39] and nitroalkenes[40] (Table 2).



Scheme 13

Table 2



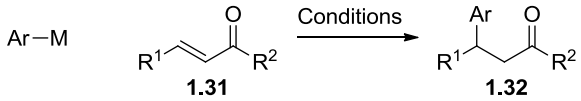
1.30 **1.37** **1.38**

Entry	X	Conditions	**1.38** [%]	*ee* [%]
1	C(O)OR	$ArB(OH)_2$ (2-5 eq), $Rh(acac)(C_2H_4)_2$ (3 mol/%), **(*S*)-1.34** (4.5 mol/%), dioxane:H_2O 6:1, 100 °C, 16 h	26-98 10 examples	77-92[37]
2	C(O)NHR	$ArB(OH)_2$ (2 eq), $Rh(acac)(C_2H_4)_2$ (3 mol/%), **(*S*)-1.34** (4.5 mol/%), K_2CO_3 (0.5 eq), dioxane:H_2O 6:1, 100 °C, 16 h	19-90 11examples	77-95[38]
3	$P(O)OR_2$	$(ArBO)_3$ (3.3 eq), $Rh(acac)(C_2H_4)_2$ (3 mol/%), **(*S*)-1.34** (3.3 mol/%), H_2O (10 eq), dioxane, 100 °C, 3 h	39-96 10 examples	91-99[39]
4	NO_2	$ArB(OH)_2$ (5-10 eq), $Rh(acac)(C_2H_4)_2$ (3 mol/%), **(*S*)-1.34** (3.3 mol/%), dioxane:H_2O 10:1, 100 °C, 3 h	33-89 9 examples	38-99[40]

Other nucleophiles that have been employed in rhodium catalysed 1,4-arylations include aryl stannanes (Entry 1, Table 3),[41] various aryl silicon reagents (Entries 2, 3, 4 and 5)[42-45] triphenyl bismuth (Entry 6),[46] aryl titanium reagents (Entry 7)[47] and aryl lead compounds (Entry 8).[48] Almost all these reactions use water as a co-solvent with two examples (Entries 5

and 8) being run solely in water. However, there are fewer examples of asymmetric 1,4-addition using these nucleophiles rather than organoboron nucleophiles.

Table 3



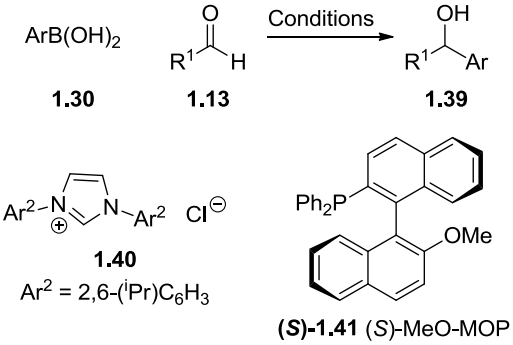
1.31 **1.32**

Entry	ArM	Eq	Conditions	**1.32** [%]	*ee* [%]
1	$ArSnMe_3$	1.2	$[Rh(cod)(MeCN)_2]BF_4$ (2 mol/%), H_2O (1 eq), THF, 60 °C, 2-20 h	60-98 10 examples[41]	-
2	$ArSiEt(OH)_2$	0.3	$[Rh(OH)(cod)]_2$ (3 mol/%), THF, 70 °C, 24 h	61-99 9 examples[42]	-
3	$ArSi(OMe)_3$		$[Rh(cod)(MeCN)_2]BF_4$ (2 mol/%), dioxane:H_2O 10:1, 90 °C, 20 h	73-93 5 examples[43]	-
4	$ArSi(OR)_3$	2	$[Rh(cod)(MeCN)_2]BF_4$ (4 mol/%), **(*S*)-1.34** (6 mol/%), dioxane:H_2O 10:1, 90 °C, 20 h	56-90 8 examples	75-98[44]
5	$ArSiPhCl_2$	4	$[Rh(cod)_2]BF_4$ (5.2 mol/%), NaF (20 eq), H_2O, 100 °C, 12 h	34-97 11 examples[45]	
6	$ArBiPh_2$	1.1	$[Rh(cod)Cl]_2$ (5 mol/%), H_2O:THF 7:3, 50 °C, 12 h	40-84 4 examples[46]	
7[a]	$ArTi(O^iPr)_3$	1.6	$[Rh(OH)(($**(*S*)-1.34**$))]_2$ (1.5 mol/%), THF, 20 °C, 1 h	62-89 8 examples	94->99[47]
8	$ArPbMe_3$	1.4	$[Rh(cod)_2]BF_4$ (10 mol/%), H_2O, 70 °C, 15 h	66-68 2 examples[48]	-

[a] Isolated as silyl enol ether.

Addition of organometallic nucleophiles to carbonyl compounds in a 1,2-fashion to give secondary alcohols, is another area of research for rhodium catalysis. Although additions of Grignard reagents are possible, rhodium catalysis allows for milder conditions to be used and more sensitive functional groups present in the reactant. As with 1,4-conjugate additions, boron nucleophiles have been the organometallic reagent of choice. Again, Miyaura *et al.* reported the first example of 1,2-addition of aryl boronic acids to aldehydes in excellent yield (Entry 1, Table 4).[49] Fürstner and co-workers used rhodium catalysis with a *N*-heterocyclic carbene ligand derived from **1.38** to give good conversions, including excellent chemoselectivity with a ketone containing substrate (Entry 2).[50] However, achieving enantioselectivity with these additions has proved more elusive than with 1,4-additions; Miyaura found only a 41% enantiomeric excess after a small ligand screen (Entry 3).[49]

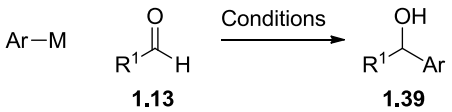
Table 4



Entry	Conditions	**1.39** [%]	*ee* [%]
1	$ArB(OH)_2$ (2 eq), $Rh(acac)(CO)_2$ (3 mol/%), dppf (3 mol/%), DME:H_2O 1:1, 80 °C, 16 h	31-97 15 examples[49]	-
2	$ArB(OH)_2$ (2 eq), $RhCl_3.H_2O$ (1 mol/%), **1.40** (1 mol/%), NaOMe (1 eq), DME H_2O 4:1, 80 °C, 30 min	52-99 13 examples[50]	
3	$ArB(OH)_2$ (2 eq), $[Rh(acac)(C_2H_4)_2]$ (3 mol/%), **(*S*)-1.41** (3 mol/%), DME:H_2O 1:1, 60 °C, 36 h	78% 1 example	41% (*R*)[49]

Again additions are not limited to organoboron compounds, with trimethylphenyl stannane (Entry 1, Table 5),[51] and aryl silicon reagents also being used (Entries 2 and 3).[52,53]

Table 5



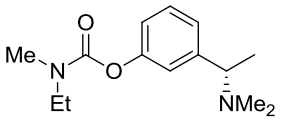
Entry	ArM	Eq	Conditions	**1.39** [%]
1	$ArSnMe_3$	1	$[Rh(cod)_2]BF_4$ (5 mol/%), NaF (5 eq), H_2O, 110 °C, 12 h	52-92 11 examples[51]
2	$ArSiMeF_2$	2	$[Rh(cod)(MeCN)_2]BF_4$ (2 mol/%), KF (3 eq), THF, 60 °C, 18-20 h	70-100 12 examples[52]
3	$ArSiEt(OH)_2$	2	$[Rh(OH)(cod)]_2$ (3 mol/%), dioxane, 70 °C, 24 h	47-87 4 examples[53]

These are just two examples of the types of unsaturated substrates which can be used for rhodium catalysed carbon-carbon bond formation. Over the next three chapters, many examples of rhodium catalysed additions to imines substrates will be reviewed.

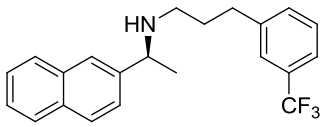
Chapter 2

2.1 Chiral Arylethanamines

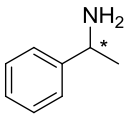
A particular class of α-chiral amines of interest are chiral arylethanamines. Chiral arylethanamines are present as single enantiomers in pharmaceutical products such as Rivastigmine[54] and Cinacalcet[55] (Scheme 14). α-Methylbenzylamine **2.1a** is one of the most widely used resolving agents for resolving racemic acids *via* formation of diastereomeric salts.[56] α-Methylbenzylamine **2.1a** can itself be simply resolved with tartaric acid.[57,58] However, resolution is often not an efficient or particularly general method, so research has been ongoing towards a catalytic asymmetric synthesis of enantioenriched arylethanamines. The main points of this research will now be discussed.



Rivastigmine (Exelon®)
Novartis
Alzheimer's/Parkinson's



Cinacalcet (Mimpara®)
Amgen
Hyperparathyroidism



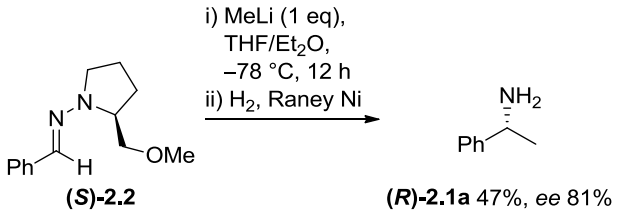
2.1a

Scheme 14

2.2 Methyl Addition to Aldimines

2.2.1 Methyllithium

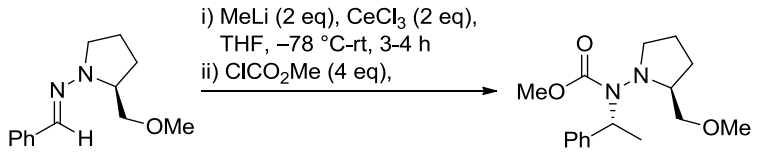
Methyllithium is both a highly nucleophilic and highly basic reagent and this limits the range of functional groups that can be present in the substrates with which it is reacted in enantioselective fashion owing to achiral background or side reactions. It is commercially available as an ethereal solution, although it can also be made by treating methyl bromide with lithium. Initial studies into the addition of methyllithium to imines used a chiral auxiliary as the source of chirality.



(*S*)-2.2 **(*R*)-2.1a** 47%, *ee* 81%

Scheme 15

Enders and co-workers reported the first synthesis of an enantioenriched amine **(*R*)-2.1a** using a chiral auxiliary approach (Scheme 15).[59] Diastereoselective addition of methyllithium to SAMP hydrazone **(*S*)-2.2** followed by cleavage of the auxiliary (which can be recycled) using hydrogenolysis gave (*R*)-phenylethylamine **(*R*)-2.1a** in moderate yield and good enantioselectivity. Using the equivalent RAMP hydrazone allows access to **(*S*)-2.1a**.



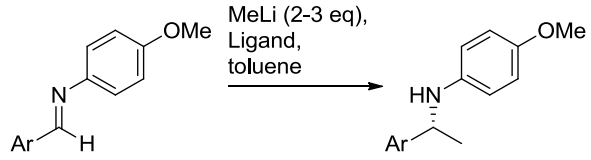
(*S*)-2.2 **(*S,R*)-2.3** 59%, *dr* 91:9

Scheme 16

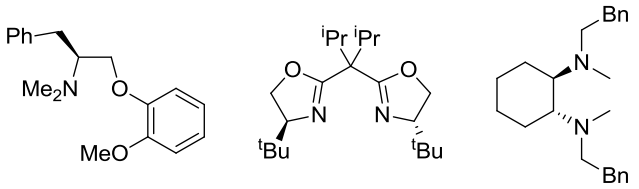
Similarly, Denmark *et al.* added organocerium reagents to SAMP hydrazone **(*S*)-2.2** (Scheme 16).[60] The methylcerium reagent was formed *in situ* from methyllithium and anhydrous cerium(III) chloride and is less basic than its precursor allowing hydrazones with enolisable protons to be used.[61] The carbamate **(*S,R*)-2.3** was formed to prevent oxidation of the resulting hydrazine and the free amine could be obtained by hydrogenolysis as before.

The breakthrough first methyl addition to an achiral imine using a chiral ligand was reported by Tomioka *et al.* in 1990.[62] The addition of methyllithium to a *p*-methoxyphenyl imine **2.4** in the presence of chiral amino-ether **(*S*)-2.6** in stoichiometric quantities gave enantioenriched amine **2.5** in good enantiomeric excess (Entry 1, Table 6). Substoichiometric quantities of the ligand **(*S*)-2.6** can be used, however, the enantiomeric excess is lowered (Entry 2).[63-66] The ligand-methyllithium complex is more reactive than the uncoordinated methyllithium reagent and in the absence of the ligand the conversion is lower. Denmark *et al.* used a C_2-symmetric *bis*-oxazoline ligand **(*S,S*)-2.7** for this addition in good yield and enantioselectivity (Entry 3).[67] The group of Alexakis used 1,2-diamine ligands in substoichiometric quantities with variable results (Entry 4).[68] The utility of this method was demonstrated in the synthesis of (*R*)-salsolidine **(*R*)-2.11** in four steps from imine **2.9** (Scheme 17).[69]

Table 6

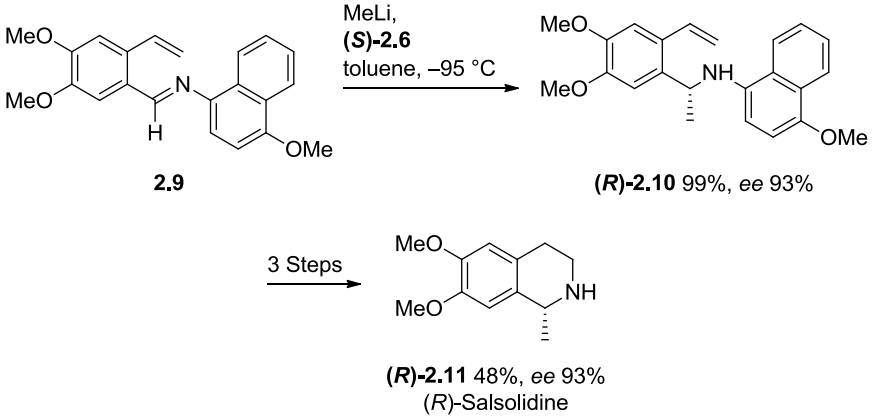


2.4 **2.5**



(*S*)-2.6 **(S,S)-2.7** **(*R*,*R*)-2.8**

Entry	Ligand	Eq	*T* [°C]	Time [h]	**2.5** [%]	*ee* [%]
1	**(*S*)-2.6**	2.6	−100	1	52-98	70-74 (*R*) 3 examples[62]
2	**(*S*)-2.6**	0.5	−42	3	96	62 (*R*)[63]
3	**(*S*,*S*)-2.7**	1	−75	1	77	89 (*R*)[67]
4	**(*R*,*R*)-2.8**	0.2	−78	15	35-98	48-74 (*R*) 6 examples[68]



2.9

(*R*)-2.10 99%, *ee* 93%

(*R*)-2.11 48%, *ee* 93%
(*R*)-Salsolidine

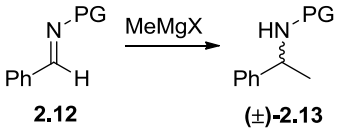
Scheme 17

2.2.2 Methyl Grignard Reagent

Methyl Grignard reagents are, like methyllithium, both highly nucleophilic and basic. They cannot be used with imines bearing enolisable protons as enolisation will be the dominant reaction and their reactivity will limit the substrate scope. Solutions of methylmagnesium

bromide in ethereal solvents are commercially available or the reagent can be freshly prepared from methyl bromide and magnesium turnings.

Table 7

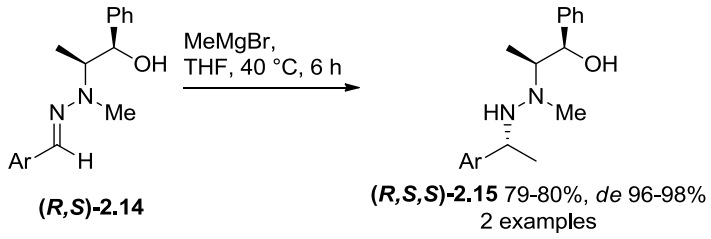


2.12 **(±)-2.13**

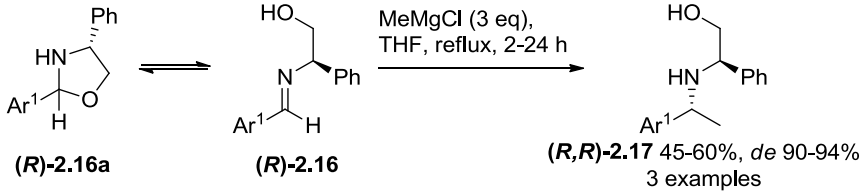
Entry	PG	MeMgX [Eq]	X	**(±)-2.13** [%]
1	$P(O)Ph_2$	3	I	63[17]
2	Ts	3	Br	84[b][70]
3	$PO(OEt)_2$	2	Br	47[a][71]

[a] Imine prepared *in situ*; [b] yield of amine following deprotection with HCl.

Addition of methyl Grignard reagents to various activated imines **2.12** gives the racemic secondary amines **(±)-2.13** in good yields (Table 7).[17,70,71] The first asymmetric methyl Grignard reagent addition was carried out by the group of Takahashi in 1979 using a chiral auxiliary approach employing *N*-methyl ephedrine (Scheme 18).[72]

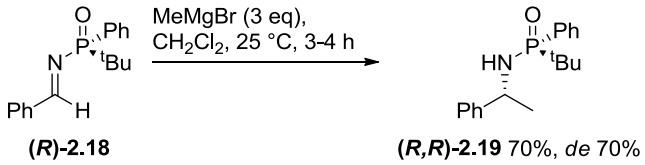


Scheme 18



Scheme 19

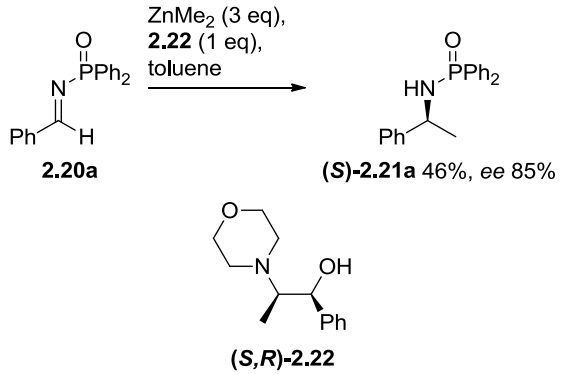
Pridgen *et al.* used a chiral oxazolidine **(*R*)-2.16a** for diastereomeric methyl Grignard reagent additions (Scheme 19).[73] Colobert *et al.*[20,74] have developed a *P*-chirogenic *N*-phosphinoylimine **(*R*)-2.18** (Scheme 20) and have achieved some encouraging diastereoselectivity with the addition of methyl Grignard reagent to give amine **(*R,R*)-2.19**.



Scheme 20

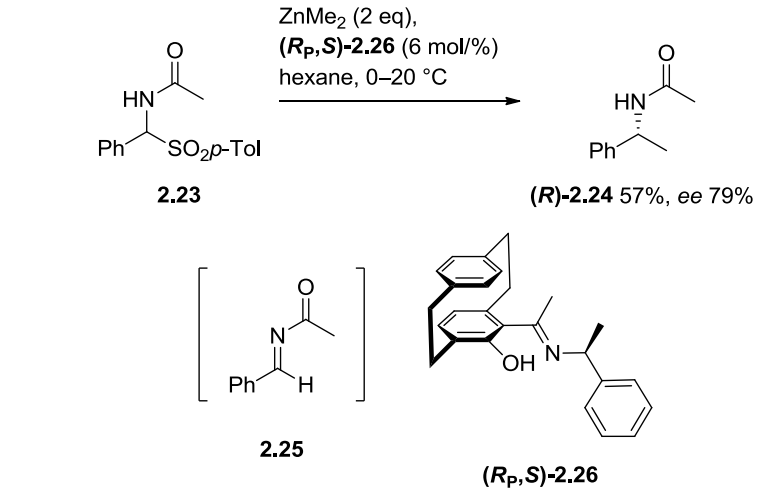
2.2.3 Dimethylzinc

Dialkylzinc reagents have a lower nucleophilicity than alkyllithium or alkyl Grignard reagents as the carbon-metal bond is far less polarised. This gives dialkylzinc reagents the advantage of wider range of functional group tolerance in both the substrate and any ligands used. However, as they are less nucleophilic, the imines used need to be more electrophilic. Coordination of the dialkylzinc with a Lewis basic ligand causes deviation from the normal linear geometry at zinc and increases the nucleophilicity of the alkyl groups. There are many examples of additions of diethylzinc to activated imines, however, due to its lower reactivity, there are fewer examples using dimethylzinc and often more equivalents are needed in comparison with diethylzinc.



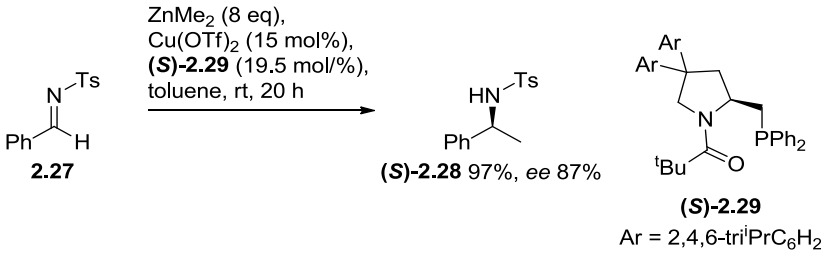
Scheme 21

Soai *et al.* reported the first addition of dimethylzinc to imine **2.20a** in their landmark paper of 1992 (Scheme 21).[75] The chiral amino-alcohol **(*S*,*R*)-2.22** was used in stoichiometric amounts to activate the zinc reagent and give good enantioselectivities. An example using an external [2.2]paracyclophane based *N*,*O*-ligand **(R_P,*S*)-2.26** in catalytic quantities was reported by the group of Bräse (Scheme 22).[13] The *N*-acyl imine **2.25** was formed *in situ* from sulfinate precursor **2.23**.



Scheme 22

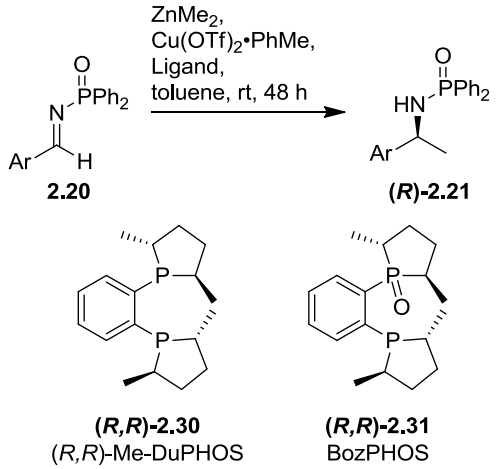
Transmetallation with a transition metal is another strategy for increasing the nucleophilicity of the alkyl groups of dialkylzinc reagents. Copper has been the most extensively used transition metal.[76] Tomioka *et al.* investigated a chiral amidophosphine ligand **(*S*)-2.29** and a copper catalyst system for the alkylation of *N*-sulfonyl imines **2.27** (Scheme 23). Methylation occurred in excellent yield and enantiomeric excess, however, eight equivalents of dimethylzinc were required.[77]



Scheme 23

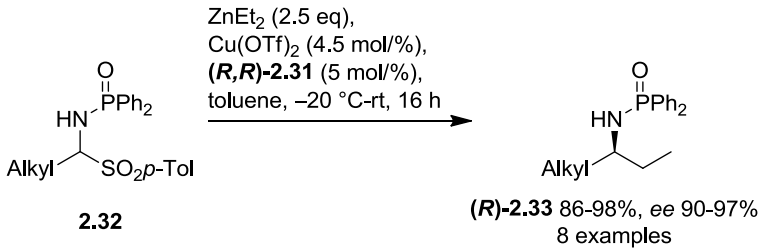
The Charette group have developed a copper catalysed system for the catalytic asymmetric addition of dimethylzinc to diphenylphospinoyl protected aryl imines **2.20**, initially using (*R,R*)-Me-DuPHOS **(*R,R*)-2.30** (Entry 1, Table 8).[78] Subsequently, it was found that using the novel (*R,R*)-Me-DuPHOS monoxide (BozPHOS) ligand **(*R,R*)-2.31** allowed the number of equivalents of dimethylzinc to be greatly reduced whilst the yield of **(*R*)-2.21** increased (Entry 2).[79] The BozPHOS ligand **(*R,R*)-2.31** can be prepared from (*R,R*)-Me-DuPHOS in three steps with a 90% overall yield.[79]

Table 8

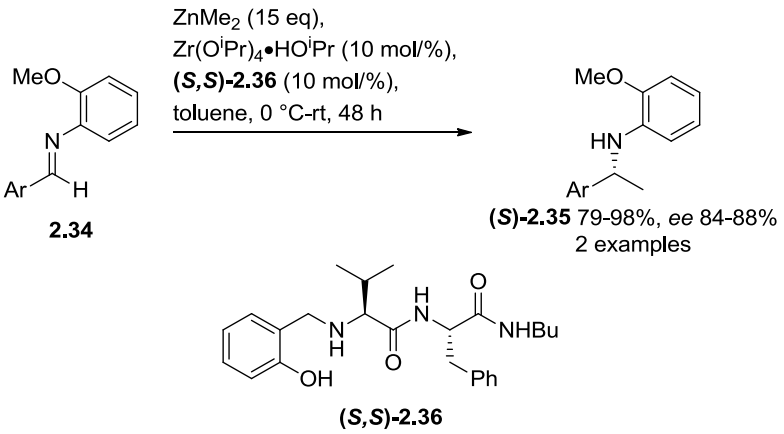


Entry	Ligand	Ligand [mol/%]	$ZnMe_2$ [Eq]	$Cu(OTf)_2$•PhMe [mol/%]	**(*R*)-2.21** [%]	*ee* [%]
1	**(*R,R*)-2.30**	10	10	10	51	90[78]
2	**(*R,R*)-2.31**	5	5	5	80-90%	89-97% 3 examples[79]

Charette has also reported ethyl addition to *N*-phosphinoylalkylimines (Scheme 24).[80] The addition to alkylimines is normally problematic due the α-enolisable protons. Charette avoids these problems by generating the imine *in situ* from a sulfinate adduct **2.32** and an extra equivalent of the organozinc reagent.

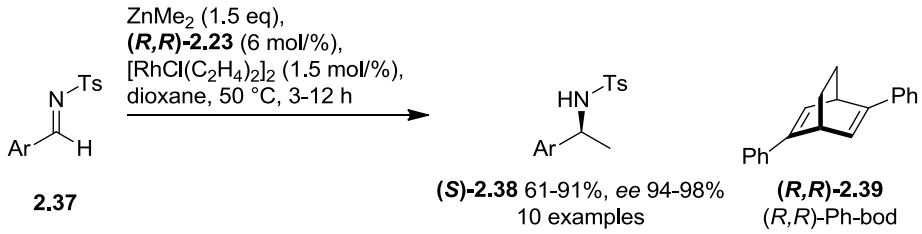


Scheme 24



Scheme 25

Hoveyda *et al.* described a zirconium-catalysed imine alkylation (Scheme 25) using a peptide based chiral ligand **(*S,S*)-2.36** to afford enantioenriched arylimines **(*S*)-2.35** in good yields and enantioexcesses although again high dimethylzinc loadings were need to give these yields.[81] Hayashi's group found rhodium complexes coordinated with chiral diene ligands to be efficient in the asymmetric addition of aryl boronic acids to imines (see Section 3.2.6.1). Initial attempts at methylation with methyl boronic acid failed, but it was found that dimethylzinc gave excellent results in the system using chiral diene ligand **(*R,R*)-2.39** (Scheme 26);[82] this was the first example of a rhodium catalysed methylation. A variety of substituted *N*-tosylarylimines was looked at and it was found that electron-donating or *ortho*-substituents required longer reaction times. The protecting tosyl group was removed by treatment with lithium in liquid ammonia to give the amine in 79% yield with no racemisation.[82]

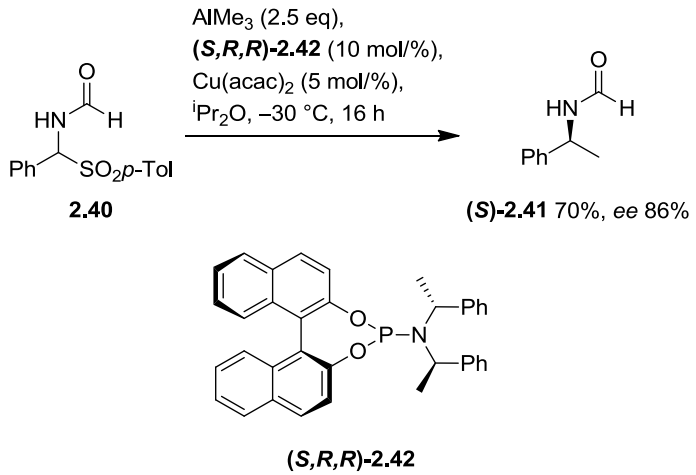


Scheme 26

2.2.4 Trimethylaluminium

Feringa *et al.* found that dimethylzinc was not effective under the conditions they had developed for diethylzinc addition to *N*-formyl imines. However, a little optimisation lead to

conditions under which trimethylaluminium could be used as the methyl source (Scheme 27).[83]



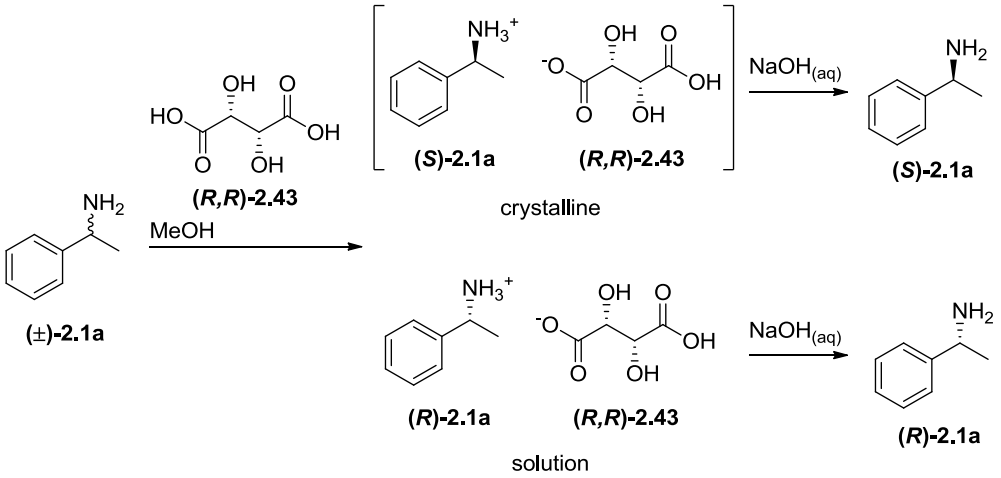
Scheme 27

2.3 Other Routes to Chiral Arylethanamines

2.3.1 Resolution

2.3.1.1 Classical Resolution

The crystallisation of diastereomeric salts (classical resolution) is a important method for the resolution of arylethanamines, for example **(±)-2.1a** can be resolved using (*R,R*)-tartaric acid **(*R,R*)-2.43** (Scheme 28).[57] However, the choice of the resolving agent is substrate specific and typically found by trial and error. The effectiveness of a particular acid for a range of structurally similar amines can vary dramatically.[84,85]

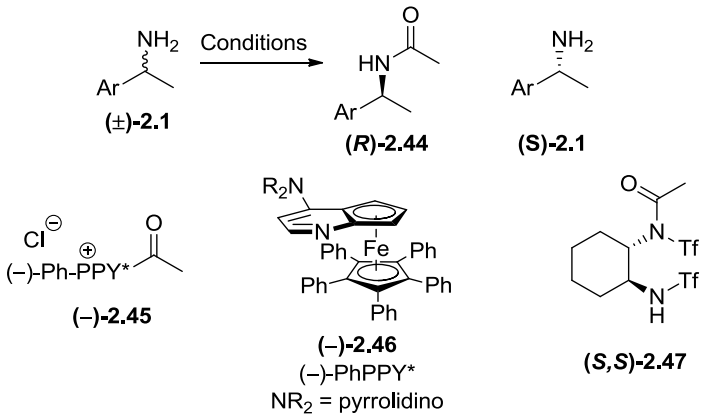


Scheme 28

2.3.1.2 Chemocatalytic Kinetic Resolution

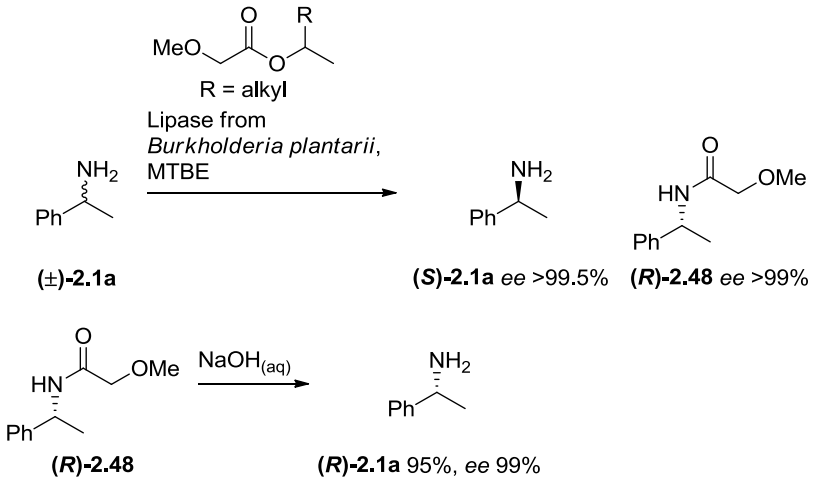
Another method for resolving enantiomers is kinetic resolution, which takes advantage of the different reaction rates of enantiomers with an enantiopure reagent *via* diastereomeric transition states. Fu *et al.* have used a chiral acylating agent **(−)-2.45** formed by *N*-acylation of planar chiral DMAP derivative **(−)-2.46** to give acetamides **2.44** in good enantiomeric excess (Entry 1, Table 9),[86] however, a high ratio of racemic amine to acylating agent is needed. A much lower ratio was used by the group of Blackmond with their acylating agent **(*S*,*S*)-2.47** (Entry 2),[87] but improvements need to be made for chemocatalytic kinetic resolution to be a practical route to enantioenriched arylethanamines.

Table 9



Entry	Conditions	**2.44** *ee* [%]
1	**(±)-2.1** (8 eq), **(−)-2.45** (1 eq), CH_2Cl_2, −78 °C	81-91 (*R*) 5 examples[86]
2	**(±)-2.1** (1 eq), **(*S*,*S*)-2.47** (0.5 eq), $^{n}Oct_3NMeCl$ (12.5 eq), THF, −20 °C	94 (*S*)[87]

2.3.1.3 Enzymatic Kinetic Resolutions

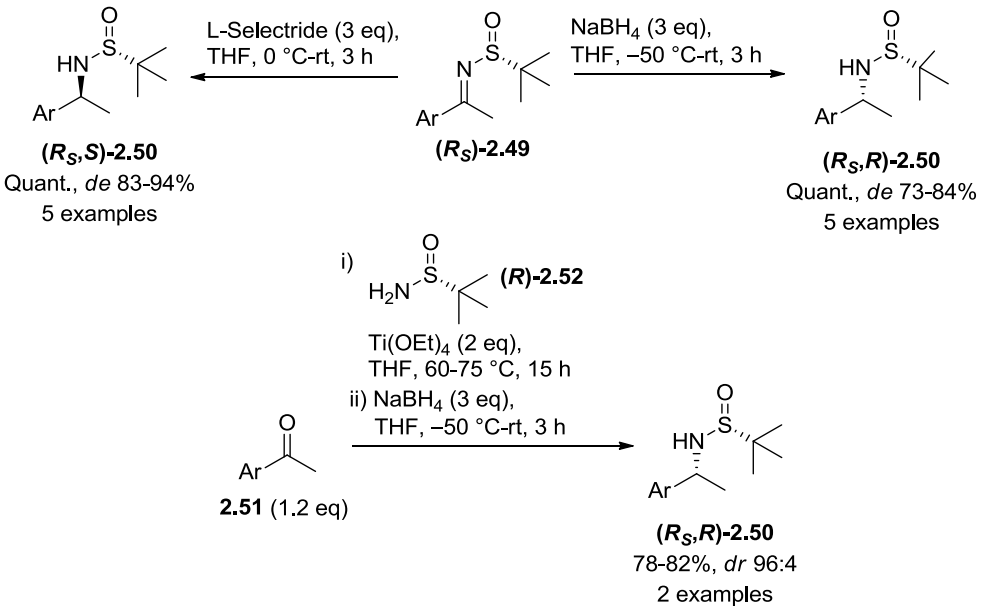


Scheme 29

A biocatalytic resolution method used for the industrial preparation (> 1000 tonnes yr^{-1}) of enantioenriched amines is shown in Scheme 29.[4] A bacterial lipase was found to efficiently catalyse the enantioselective acylation of α-methylbenzylamine **(±)-2.1a**. Hydrolysis of the amide **(*R*)-2.48** with base (with no racemisation in certain solvents) allows both enantiomers to be isolated and the acylating agent to be recovered. This method was found to be applicable to a range of arylalkylamines.[88]

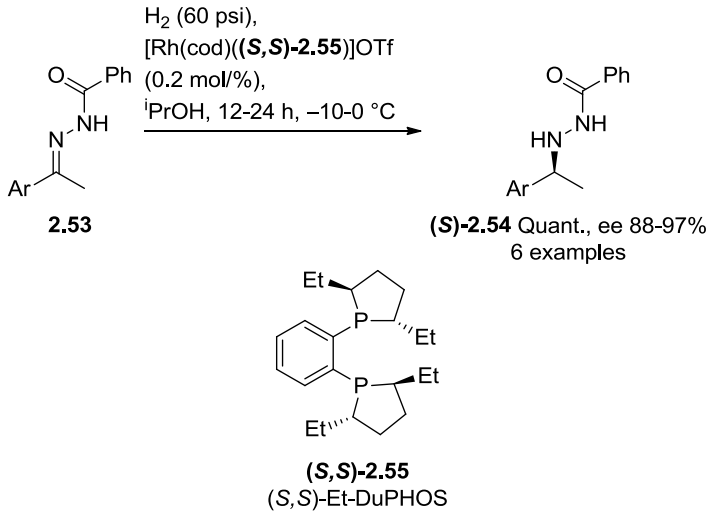
2.3.2 Reduction of Ketimines

The synthesis of enantioenriched amines can also be achieved by the addition of hydride to a ketimine. The chirality can be induced by a chiral auxiliary incorporated into the imine substrate or an external chiral ligand, ideally in catalytic quantities. Enantioselective transition metal catalysed hydrogenation of enamine or enamide substrates is another strategy to access arylmethylamines[5] which will not be discussed here.



Scheme 30

The *N*-*tert*-butylsulfinyl chiral auxiliary developed by Ellman has been utilised in reductive approaches to enantioenriched amines. It was found that the diastereoselectivity of the reduction of *N*-*tert*-butylsulfinyl ketimine **(*R*$_S$)-2.49** could be switched by changing the reducing agent from sodium borohydride to L-selectride (Scheme 30).[89] Ellman and co-workers also found that the amine **2.50** could be made in one-pot from the ketone **2.51** using a diastereoselective reductive amination (Scheme 30), and again the diastereoselectivity was dependent on the reductant.[90,91]

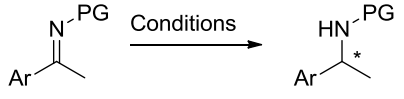


Scheme 31

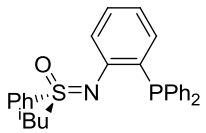
Another approach is the asymmetric hydrogenation of prochiral ketimines with transition metal catalysis. In 1994 Burk *et al.* investigated the rhodium catalysed asymmetric hydrogenation of *N*-benzoylhydrazones **2.53** (Scheme 31).[92] The high enantioselectivities are explained by the

presence of the carbonyl group which can chelate to the metal centre. The free amine can be obtained by treatment of **(*S*)-2.54** with samarium(II) iodide.

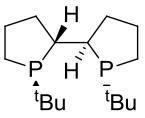
Table 10



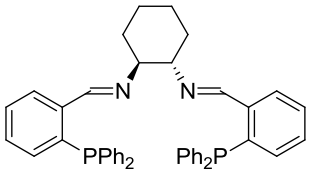
2.56 **2.57**



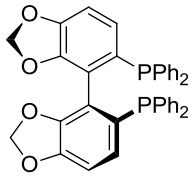
(*S*)-2.58



(*S,S,R,R*)-2.59
(*S,S,R,R*)-TangPhos



(*S,S*)-2.60

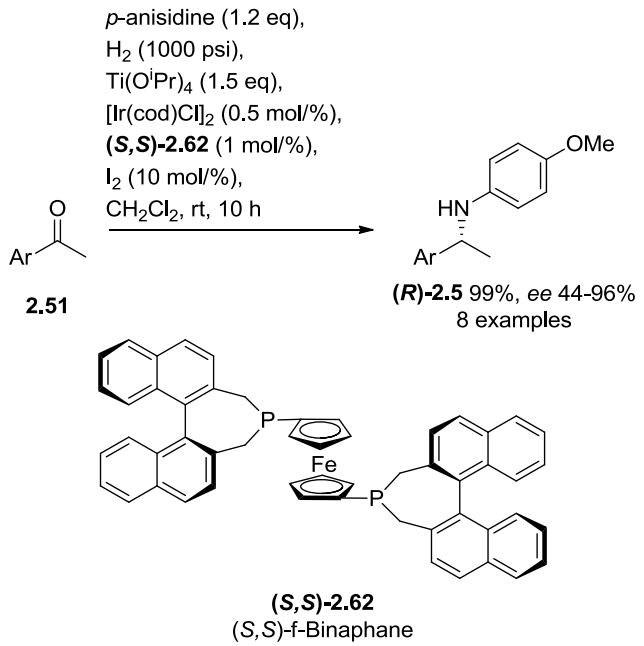


(*S*)-2.61
(*S*)-segphos

Entry	PG	Conditions	**2.57** [%]	*ee* [%]
1	4-$MeOC_6H_4$	H_2 (20 bar), $[Ir(cod)Cl]_2$ (0.5 mol/%), **(*S*)-2.58** (1.1 mol/%), I_2 (2 mol/%), toluene, rt, 4-6 h	Quant 10 examples	69-98[a][93]
2	Ts	H_2 (75 atm), $Pd(OCOCF_3)_2$ (1 mol/%), **(*S,S,R,R*)-2.59** (1.2 mol/%), CH_2Cl_2, 40 °C, 24 h	Quant 9 examples	96->99 (*R*)[94]
3	Ts	H_2 (1000 psi), $Pd(OCOCF_3)_2$ (2 mol/%), **(*S*)-2.61** (2.4 mol/%), 4 Å M.S., TFE, rt, 8 h	70-98 8 examples	93-99 (*S*)[95]
4	$P(O)Ph_2$	H_2 (1000 psi), $Pd(OCOCF_3)_2$ (2 mol/%), **(*S*)-2.61** (2.4 mol/%), 4 Å M.S., TFE, rt, 8-12 h	70-98 6 examples	93-99 (*S*)[96]
5	$P(O)Ph_2$	H_2 (600 psi), $[Et_3NH][HFe_3(CO)_{11}]$ (0.33-1.33 mol/%), **(*S,S*)-2.60** (1-5 mol/%), KOH (5 mol/%), ^{i}PrOH, 45 °C, 0.5 h	85-98 10 examples	94-98 (*R*)[97]

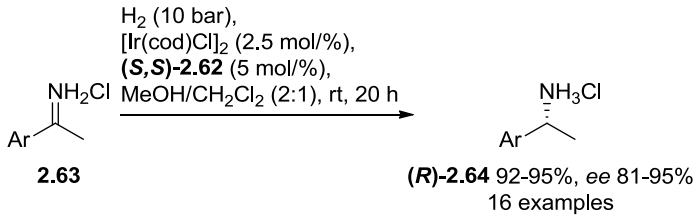
[a] Absolute stereochemistry not determined.

More recent examples of asymmetric catalytic hydrogenation include the Bolm group's iridium catalysed reduction of *N*-*p*-methoxyphenylimines (Entry 1, Table 10).[93] Zhang and Zhou's groups have developed palladium catalysed systems (Entries 2-4).[94-96] Beller *et al.* have used an iron complex to good effect.[97]



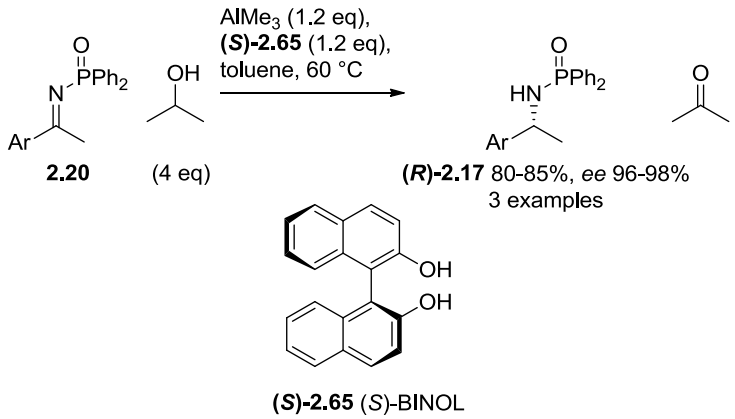
Scheme 32

An enantioselective reductive amination has been reported by the group of Zhang using *p*-anisidine as the nitrogen source (Scheme 32).[98] The iridium complex used does not hydrogenate the starting acetophenone under the reaction conditions.



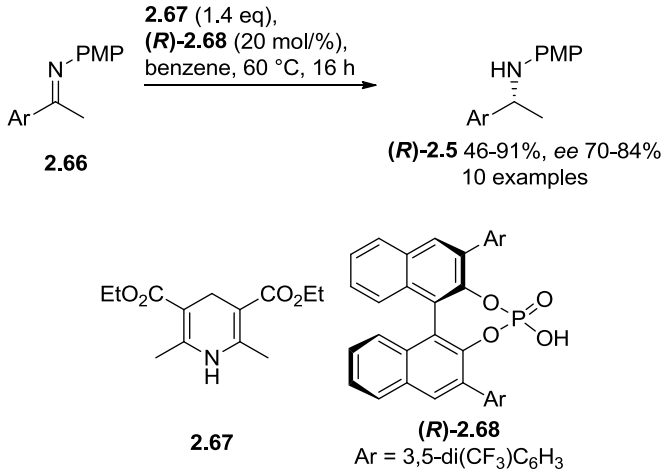
Scheme 33

An interesting development has been made by the group of Gosselin using unprotected acetophenone imines **2.63** (Scheme 33).[99] The imines are prepared by methyl Grignard reagent addition to benzonitriles. Ferrocene-based ligand **(*S,S*)-2.62** with iridium as a catalyst was found to give excellent conversions and enantioselectivities across a wide range of aryl substitution.



Scheme 34

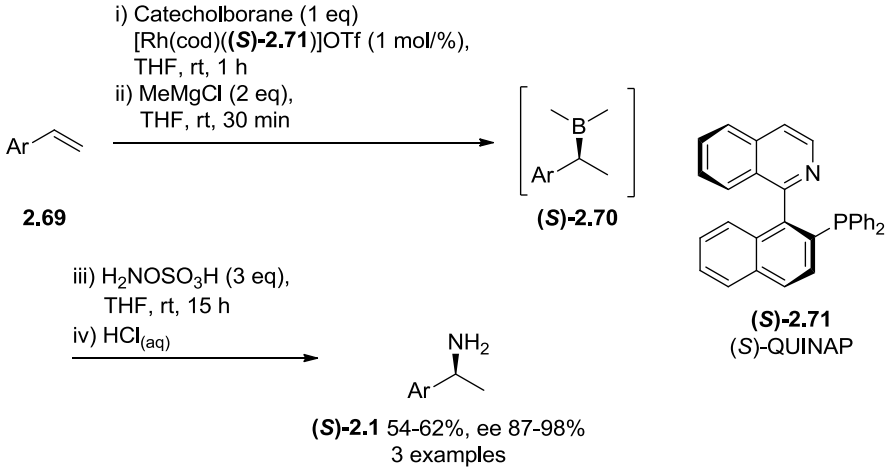
An enantioselective Meerwein-Schmidt-Ponndorf-Varley reaction using *N*-diphenylphospinoyl ketimines **2.20** was reported Scheidt (Scheme 34).[100] The hydride source is 2-propanol which forms a chiral complex with (*S*)-BINOL **(*S*)-2.65** and trimethylaluminium. A disadvantage of this approach is the stoichiometric quantity of ligand required.



Scheme 35

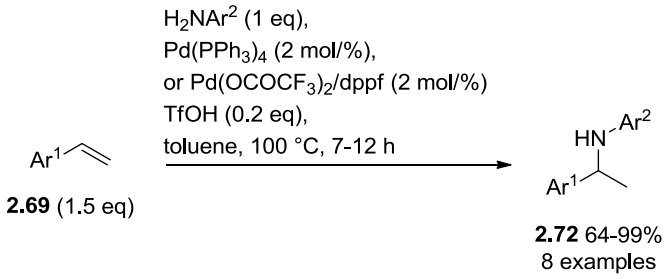
Rueping *et al.* have developed the first enantioselective Brønsted acid catalysed imine reduction (Scheme 35).[101] The chiral acid **(*R*)-2.68** is the derived from BINOL and the hydride source is Hantzsch dihydropyridine **2.67**.

2.3.3 Hydroamination



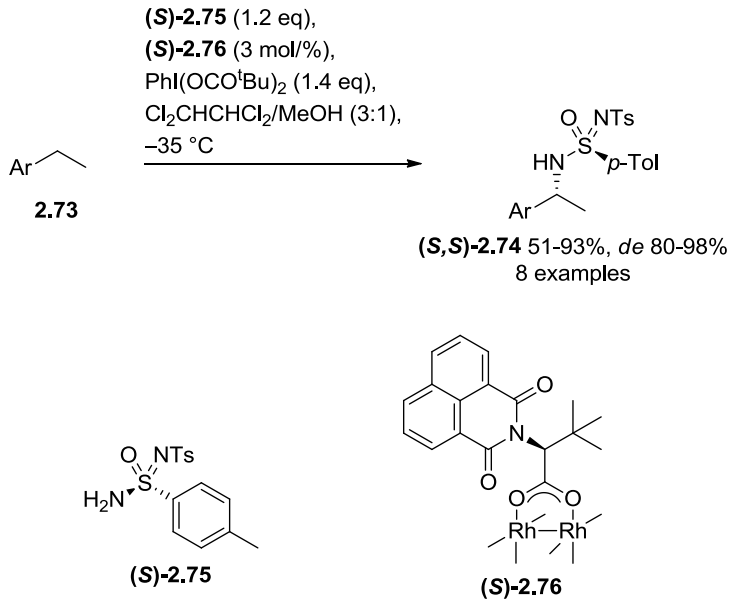
Scheme 36

Brown *et al.* have developed a one-pot synthesis of enantioenriched amines **(*S*)-2.1** from styrene derivatives **2.69** *via* trialkyl boranes **(*S*)-2.70** (Scheme 36).[102] Initially the catacholboronate is formed by asymmetric rhodium catalysed hydroboration, this is then converted to the trialkyl borane **(*S*)-2.70** before a reaction with the aminating agent, hydroxylamine-*O*-sulfonic acid. The palladium catalysed hydroamination of substituted styrenes **2.69** with anilines has be reported by the group of Hartwig (Scheme 37).[103] The was no report of the anti-Markovnikov product and an initial trial with a chiral ligand suggests that this could be developed into an asymmetric process.



Scheme 37

2.3.4 C-H Activation



Scheme 38

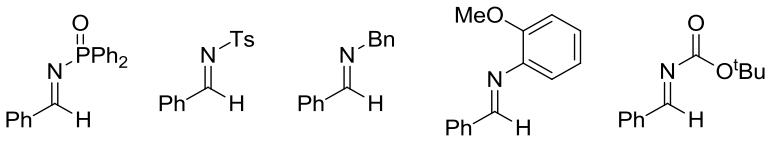
An intermolecular C-H amination is an active area of current research, to this end Müller *et al.* have developed the above process (Scheme 38).[104,105] Chiral sulfonimidamides **(*S*)-2.75** react with the hypervalent iodine component to give a iminoiodane species, this forms a rhodium-nitrene complex which inserts into the C-H bond. The sulfonimidoyl group can be removed from **(*S*,*S*)-2.74** to give the free amine, with no epimerisation, by reaction with sodium naphthalenide, or Boc protection followed by magnesium in methanol.

2.4 Results and Discussion

2.4.1 Aims and Objectives

The aim of the research discussed in this Chapter was to develop a catalytic asymmetric 1,2-addition of methyl nucleophiles to arylaldimines. The requirements of the reaction were defined as having a conveniently short reaction time, using commercially available ligands, catalyst precursors and reagents, utilising an activating group that could be mildly removed to give the free amine and being compatible with a range of substituted arylaldimines.

2.4.2 Background Work[106]

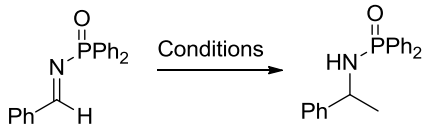


2.20a **2.27** **2.77** **2.34a** **2.78**

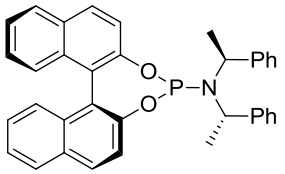
Scheme 39

Initially a range of protected imines (Scheme 39) was prepared from benzaldehyde and screened by Samir El Hajjaji.[106] From these *N*-diphenylphospinoyl imine **2.20a** was found to be the most reactive and gave the highest conversions in various methyl addition systems. Initially trimethylaluminium was used as the methylating agent and an iridium species as the catalyst, this system gave good conversion but a very low enantioselectivity with Feringa's ligand **(*S,S,S*)-2.42** (Entry 1, Table 11). When a ligand screen was carried out, the highest enantioselectivity achieved was only 36% (Entry 2). A screen of iridium and rhodium catalysts with various methyl sources and a range of phosphine ligands was undertaken. The enantioselectivities were screened in a high throughput fashion using ^{31}P NMR in the presence of (1*S*)-10-camphorsulfonic acid and verified by chiral HPLC, chiral supercritical fluid chromatography or chiral gas chromatography of an amide derivative. From this screen, an alternative system was discovered using rhodium as the catalytic species and dimethylzinc as the methyl source. This system gave a much improved enantioexcess of 92% with (*R,R*)-Me-DuPHOS **(*R,R*)-2.30** as the ligand (Entry 3). From here, the scope of the reaction was to be investigated.

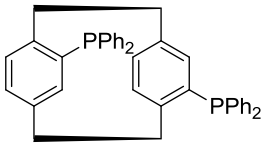
Table 11



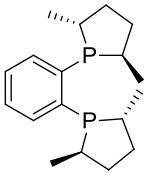
2.20a **2.21a**



(*S,S,S*)-2.42



(*R*)-2.79
(*R*)-PhanePhos



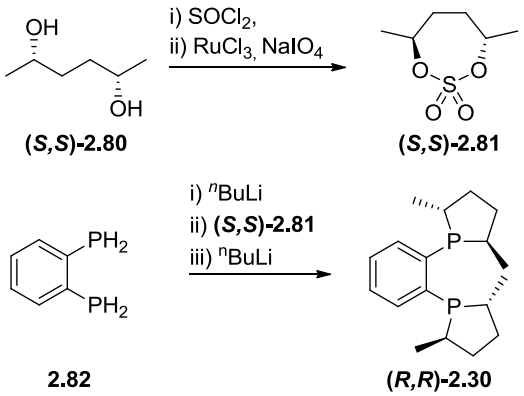
(*R,R*)-2.30
(*R,R*)-Me-DuPHOS

Entry	Methyl Source	Conditions	**2.21a** [%][a]	*ee* [%][b]
1	$AlMe_3$ (2 eq)	$[Ir(cod)Cl]_2$ (2.5 mol/%), **(*S,S,S*)-2.42** (5 mol/%), THF, rt, 24 h	96	<10
2	$AlMe_3$ (2 eq)	$[Ir(cod)Cl]_2$ (2.5 mol/%), **(*R*)-2.79** (5 mol/%), THF, reflux, 3 h	100	36
3	$ZnMe_2$ (2 eq)	$[Rh(C_2H_4)Cl]_2$ (2.9 mol/%), **(*R,R*)-2.30** (10.4 mol/%),THF, reflux, 2 h	96	93

[a] From crude ^{1}H NMR spectrum; [b] measured by chiral HPLC or SFC.

2.4.3 DuPHOS Ligand

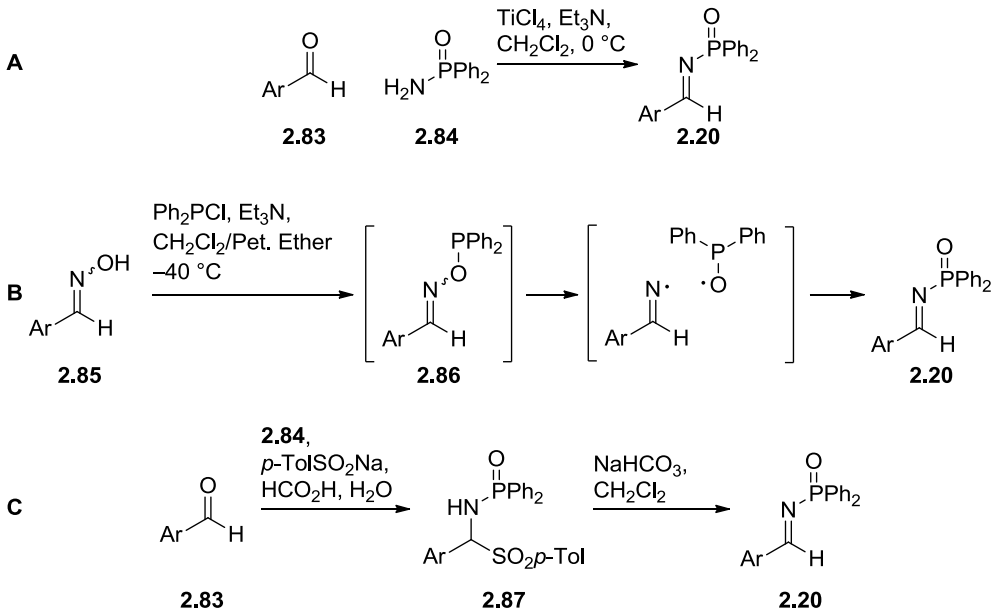
The DuPHOS family of ligands were developed by Burk in the early 1990s.[107,108] These ligands have proved to be efficient catalysts for asymmetric hydrogenation[109] and hydrosilylation. The ligands are prepared in three steps (Scheme 40), the 1,4-diol **(*S,S*)-2.80** (produced by enzymatic reduction of 2,5-hexanedione) is treated with thionyl chloride to give a cyclic sulfite which is oxidised without isolation to the sulfate **(*S,S*)-2.81**. Reaction of 1,2-*bis*(phosphino)benzene **2.82** with two equivalents of the sulfate using four equivalents of *n*-butyllithium as base provided **(*R,R*)-2.30**.



Scheme 40

2.4.4 *N*-Diphenylphosphinoylimines

N-Phosphinoylimines can be prepared in a number of ways, but for this project they have been made from the aldehyde, and diphenylphosphinic amide in the presence of triethylamine and titanium tetrachloride (Route **A**, Scheme 41).[110,111] *N*-Diphenylphosphinoylimines are stable enough to be purified by prompt column chromatography.[110,111] The titanium tetrachloride acts as a Lewis acid increasing the electrophilicity of the aldehyde to the extent that it will react with the relatively unreactive nitrogen of the phosphinamide. The low nucleophilicity of phosphinamide is due to p_{π}-d_{π} or n-σ* bonding between nitrogen and phosphorus.[112]



Scheme 41

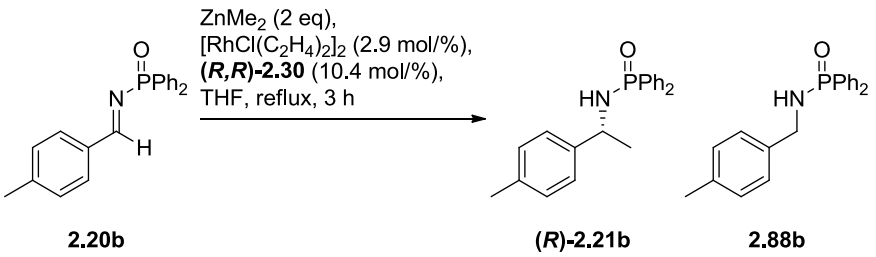
Another method for the preparation of *N*-phosphinoylimines is the reaction of an oxime **2.85** with chlorodiphenylphosphine at low temperature to give an unstable *O*-phosphinyloxime **2.86**

(Route **B**). Homolytic cleavage of N-O bond and recombination of the resulting radical pair gives the isolated product of the *N*-diphenylphosphinoyl imine.[17,113] This method of imine preparation has been reported to give variable yields of imine,[111,114] possibly dependant on the scale of the reaction.

A third route to *N*-diphenylphosphinoyl protected imines is the preparation of a sulfinyl adduct from the arylaldehyde **2.83**, diphenylphosphinic amide **2.84** and sulfinic acid (Route **C**).[80] This can then release the imine by elimination on treatment with base, either before the reaction or *in situ*. This is particularly powerful for the synthesis of aliphatic imines.

2.4.5 Further Optimisation of Dimethylzinc Addition

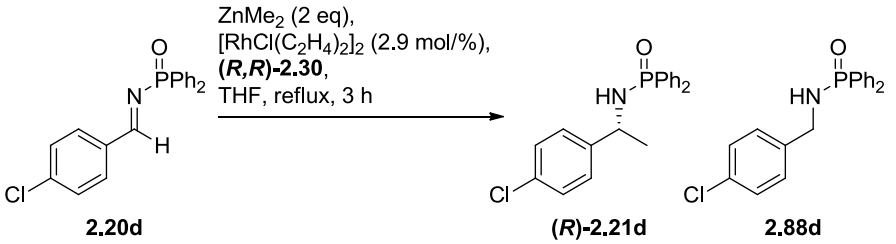
When an initial reaction of the rhodium-catalysed addition of dimethylzinc to diphenylphospinoyl protected *p*-tolyl imine **2.20b** was carried out, a small impurity was noted in the crude ^{1}H NMR spectrum. A triplet was observed at 4.09 ppm, close to the multiplet due to the α-hydrogen at 4.41-4.31 ppm. Attempts to separate this impurity from the desired product by column chromatography or crystallisation were unsuccessful. It was hypothesised that the triplet observed in the ^{1}H NMR spectra corresponded to the two benzylic hydrogens present in the reduced imine **2.88b** (Scheme 42).



Scheme 42

The mechanism of how the reduction had occurred was unclear at this stage, but the structure was confirmed by synthesis of **2.88b** from 4-methylbenzylamine and diphenylphosphinic chloride. Higher levels of impurity were observed when a lower ratio of catalyst to ligand was employed (Table 12).[106] However, if a high ratio was used the conversion decreased and the enantiomeric excess declined, therefore, an optimum ratio of 1:1.8 was settled upon (Entry 4).

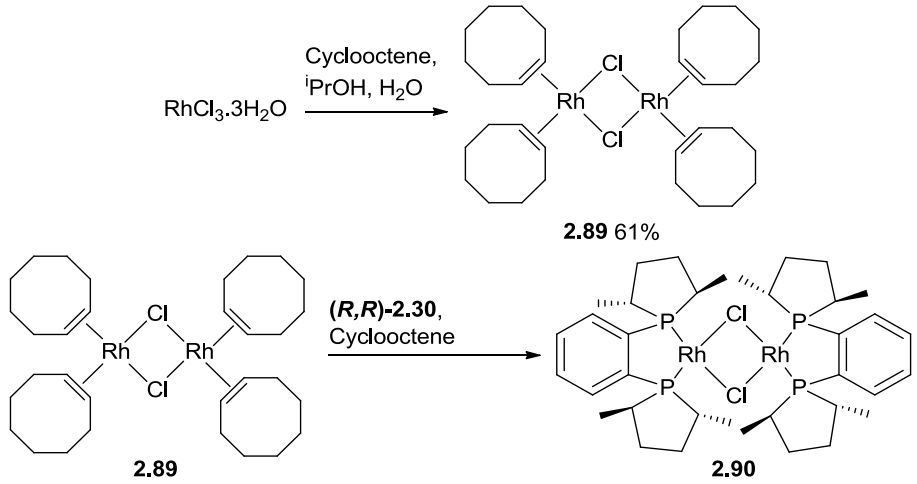
Table 12[a]



Entry	Rh:**(*R*,*R*)-2.30**	Conversion [%][b]	**(*R*)-2.21d**:**2.88d**[b]	*ee* [%][c]
1	1:0	100	10:90	0
2	1:0.9	100	88:12	91
3	1:1.4	100	92:8	82
4	1:1.8	100	95:5	86
5	1:2.2	86	94:6	80
6	1:3.0	11	72:28	78

[a] Reaction run with $[RhCl(C_2H_4)_2]_2$ (2.9 mol/%) and varying amounts of **(*R*,*R*)-2.30**; [b] from crude ^{1}H NMR spectrum; [c] determined by GC of trifluoroacetamide derivative; [d] reaction run without $[RhCl(C_2H_4)_2]_2$ or **(*R*,*R*)-2.30**.

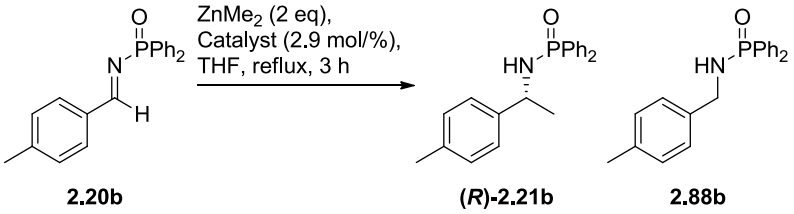
If neither (*R*,*R*)-MeDuPHOS **(*R*,*R*)-2.30** nor rhodium catalyst is present then methyl addition is the only product, but in very low conversion. This leads us to believe that the reduction is catalysed by rhodium. From the results in Table 12 it was concluded that a rhodium species not bearing a phosphine ligand is responsible for the reduction. It was hoped that if the $[RhCl(($**(*R*,*R*)-2.30**$))]_2$ **2.90** complex[115] (Scheme 43) could be synthesised, and was used to catalyse the methyl addition the side reaction would be eradicated. So first $[RhCl(coe)_2]_2$ **2.89** was prepared from rhodium(III) chloride trihydrate in 61% yield by a literature method.[116]



Scheme 43

The obtained $[RhCl(coe)_2]_2$ **2.89** could then be converted to the desired complex **2.90**. This reaction was run in various solvents; with the cleanest reaction taking place in cyclooctene (Scheme 43), in other solvents (THF, hexanes and toluene) insoluble polymeric species were isolated. When this complex was used in the catalytic reaction a disappointing result was achieved (Entry 2, Table 13), the conversion was poor and the product and impurity were formed in a 1:1 ratio. The $[RhCl(coe)_2]_2$ complex gave a result comparable to that of $[RhCl(C_2H_4)_2]_2$.

Table 13



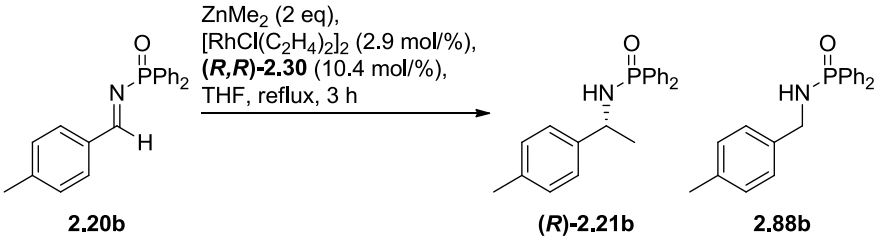
Entry	Catalyst	Conversion [%][a]	**(*R*)-2.21b**:**2.88b**[a]	*ee* [%][b]
1	$[RhCl(coe)_2]_2$[c]	75	93:7	90
2	[RhCl(**(*R,R*)-2.30**)]$_2$	29	51:49	n.d.

[a] From crude ^{1}H NMR spectrum; [b] Determined by GC of acetamide derivative; [c] 1:1.8 ratio of catalyst to **(*R,R*)-2.30**.

In the next attempt to reduce the side reaction, modifications were made to the reaction conditions. Firstly, instead of stirring the rhodium catalyst and ligand at room temperature for 30 minutes before the reaction, they were stirred at reflux for 1 hour to aid the formation of the

catalytic species. However, this led to an increase in the level of benzylamine **2.88b** (Entry 2, Table 14).

Table 14

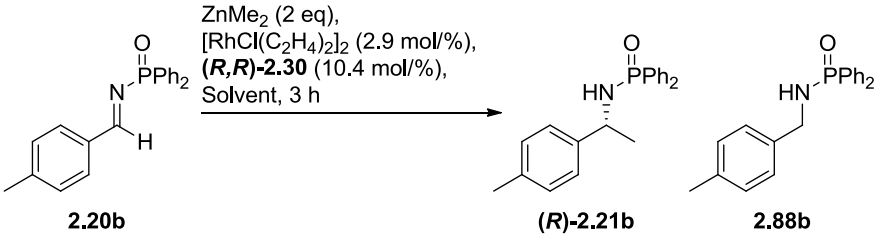


Entry	Conditions	**(*R*)-2.21b**:**2.88b**[a]
1	Normal	96:4
2	Pre-stirring ligand and catalyst at reflux 1 h	88:12
3	25 °C overnight	78:22

[a] From crude ^{1}H NMR spectrum.

The reaction was then run at the reduced temperature of 25 °C overnight (Entry 3), this lead to a marked increase in reduced imine, suggesting the reduction has a lower activation barrier that the methyl addition. Consequently, it was decided to increase the temperature, but as the standard reaction is carried out in THF at reflux, higher boiling ethers were used. The reaction was carried out at both 66 °C and reflux in each of these solvents (Table 15).

Table 15



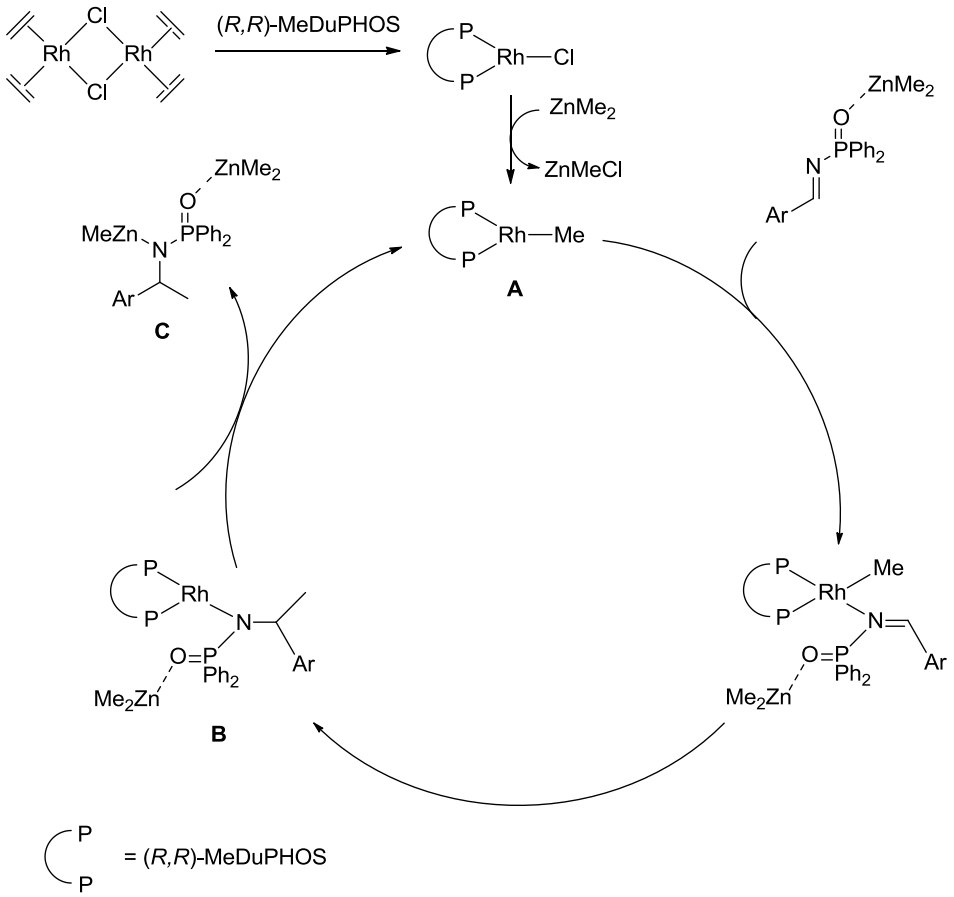
Entry	Solvent	*T* [ºC]	Conversion [%][a]	**(*R*)-2.21b**:**2.88b**[a]	*ee* [%][b]
1	Me-THF	66	40	54:46	n.d.[c]
2	Me-THF	78	0	0:100	n.d.
3	dioxane	66	57	84:16	n.d.

4	dioxane	101	75	86:14	89
5	DME	66	20	53:47	n.d.
6	DME	85	64	84:16	90

[a] From crude ^{1}H NMR spectrum; [b] determined by GC of acetamide derivative; [c] not determined.

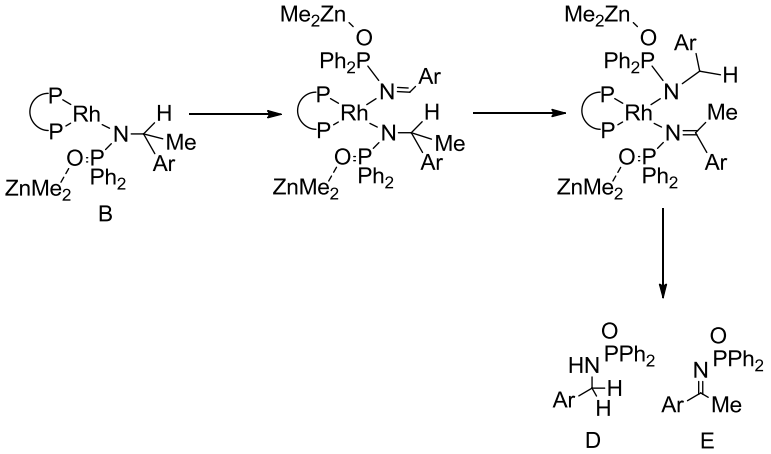
Using Me-THF the reduction reaction was favoured; in fact no methyl addition product was observed at reflux (Entry 2). Dioxane and DME gave similar results at reflux, with a slight increase in impurity and a slight decrease in enantiomeric excess (Entries 4 and 6).

The proposed catalytic cycle leading to the methyl addition product is outlined below (Scheme 44). The catalytic species **A** is formed in situ from $[RhCl(C_2H_4)_2]_2$, **(*R*,*R*)-2.30** and dimethylzinc. The imine complexes with the rhodium species, methyl addition occurs and transmetallation with dimethylzinc regenerates the catalytic complex **A** and gives species **C** that releases the product on work up.



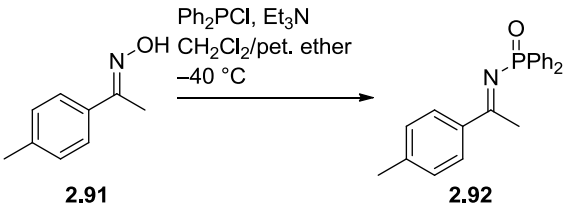
Scheme 44

Reduction is often seen when diethylzinc is used, due to β-elimination from the alkyl group. However, in the methyl case there are no β-hydrogens to be eliminated, so a different mechanism must operate. It was thought that if species **B** could complex with a second molecule of imine rather than undergoing transmetallation with dimethylzinc a hydrogen transfer could occur in a Meerwein-Varley-Ponndorf (MVP) type mechanism (Scheme 45).



Scheme 45

This type of reduction of imines does have literature precedent, for example Scheidt reports an enantioselective reduction with of *N*-phospinoyl ketimines with (BINOL)Al^{III} to give chiral amines.[100] However, in this case isopropanol is used as the hydride source. The theoretical by-product from the MVP reduction, the ketimine **2.92** was prepared from the appropriate acetophenone, *via* the oxime **2.91** (Scheme 46).[17,113] It is believed that this ketimine (and the acetophenone that it decomposes to) have been isolated after column chromatography of the crude reaction mixture as these methyl groups have been seen in the ^{1}H NMR spectra of early fractions.



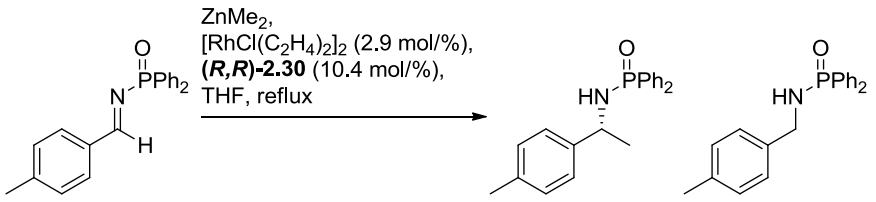
Scheme 46

We hypothesised that intermediate **B** (Scheme 44) formed in the catalytic cycle could suffer interception by further starting material imine resulting in reduction, rather than transmetallation with $ZnMe_2$ resulting in the desired product. It was found that subjecting a 1:1

mixture of methyl addition product and imine, to the normal reaction conditions did not lead to an increase in the amount of reduction product. Therefore, once the methyl addition product has formed and dissociated from the catalytic species it cannot re-associate and act as the hydride source for the MVP reduction. So if the concentration of imine in the reaction is kept low, either by slow addition or by diluting the reaction mixture the side reaction should be suppressed.

Subsequently experiments were run using a syringe pump and slowly adding a solution of the imine to a refluxing solution of dimethylzinc, catalyst and ligand, in varying volumes of THF; the results are shown in Table 16. Addition over 2 h 40 min leads to a better conversion than very slow addition over 5 h, which gave a complex mixture in which the product could not be clearly identified (Entry 2 *vs.* Entry 3). Altering the volume of THF that the reaction was carried out in had little effect on the impurity ratio (Entries 1, 2 and 4).

Table 16



Entry	Volume [mL]	$ZnMe_2$ [Eq]	Time [h][a]	Conversion [%][b]	**(*R*)-2.21**:**2.88b**[b]	*ee* [%][c]
1	3	2	2.6	55	94 : 6	n.d.[d]
2	6	2	2.6	66	95 : 5	89.3
3	6	2	5.0	0	n.d.	n.d.
4	12	2	2.6	68	96 : 4	91.4

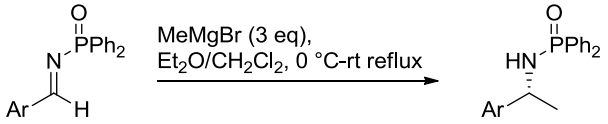
[a] Imine in THF (4 ml) added *via* syringe pump; [b] from crude ^{1}H NMR spectrum; [c] determined by GC of acetamide derivative; [d] not determined.

2.4.6 Scope of Methylation

Up to this point, most reactions had been carried out using the *p*-tolyl imine **2.20b**. As a range of substituted aryl imines were in hand, it was decided to subject these to the improved reaction

conditions. The racemate of each addition product was made by adding methylmagnesium bromide to the imine (Table 17).

Table 17

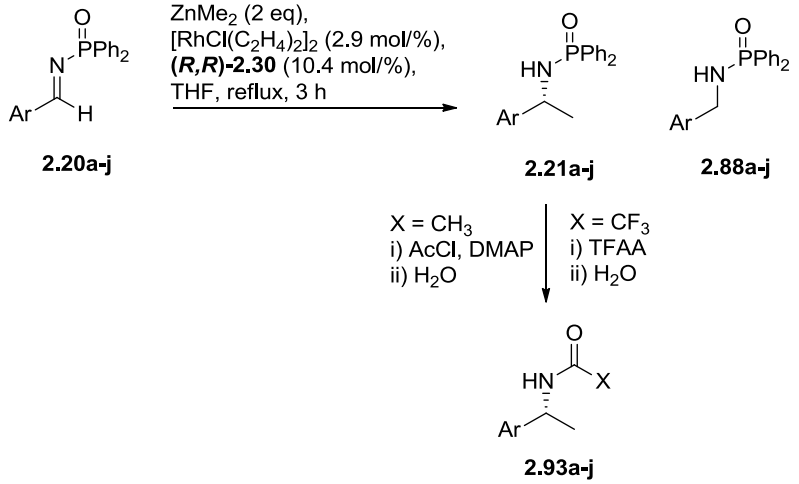


2.20 **2.21**

Entry	Ar	Substrate	**2.21** [%]	Product
1	Ph	**2.20a**	63	**2.21a**
2	4-MeC_6H_4	**2.20b**	59	**2.21b**
3	4-FC_6H_4	**2.20c**	49	**2.21c**
4	4-ClC_6H_4	**2.20d**	60	**2.21d**
5	4-BrC_6H_4	**2.20e**	65	**2.21e**
6	4-$CF_3C_6H_4$	**2.20f**	70	**2.21f**
7	3-MeC_6H_4	**2.20g**	60	**2.21g**
8	3-ClC_6H_4	**2.20h**	44	**2.21h**
9	2-MeC_6H_4	**2.20i**	34	**2.21i**
10	2-Naphthyl	**2.20j**	73	**2.21j**

Chiral gas chromatography (GC) was used to determine the enantiomeric excess as the reduction product and the desired product co-elute by HPLC. However, the diphenylphospinoyl-protected product **2.21** must first be derivatised before the GC can be run. For the majority of the products the trifluoroacetate derivative was used but in two cases the acetate was used. The addition of dimethylzinc was carried out using ten varying imines using the improved syringe pump addition conditions (Table 18).

Table 18

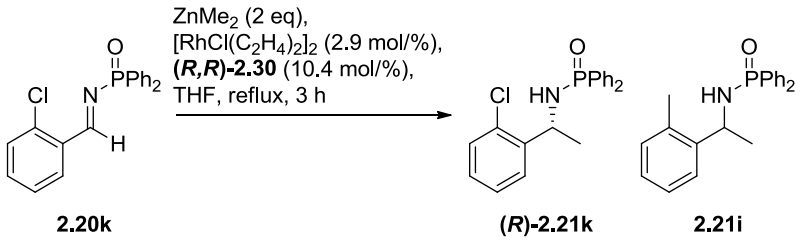


Entry	Ar	**(*R*)-2.21** [%][a]	Product	**(*R*)-2.21**:**2.88**[b]	X	*ee* [%][c]
1	Ph	63	**(*R*)-2.21a**	96:4	CF_3	93
2	4-MeC_6H_4	59	**(*R*)-2.21b**	97:3	CH_3	92
3	4-FC_6H_4	49	**(*R*)-2.21c**	94:6	CF_3	84
4	4-ClC_6H_4	60	**(*R*)-2.21d**	93:7	CF_3	86
5	4-BrC_6H_4	65	**(*R*)-2.21e**	93:7	CF_3	75
6	4-$CF_3C_6H_4$	70	**(*R*)-2.21f**	95:5	CF_3	78
7	3-MeC_6H_4	60	**(*R*)-2.21g**	95:5	CF_3	89
8	3-ClC_6H_4	44	**(*R*)-2.21h**	89:11	CF_3	78
9	2-MeC_6H_4	34	**(*R*)-2.21i**	91:9	CF_3	79
10	2-Naphthyl	73	**(*R*)-2.21j**	96:4	CH_3	84

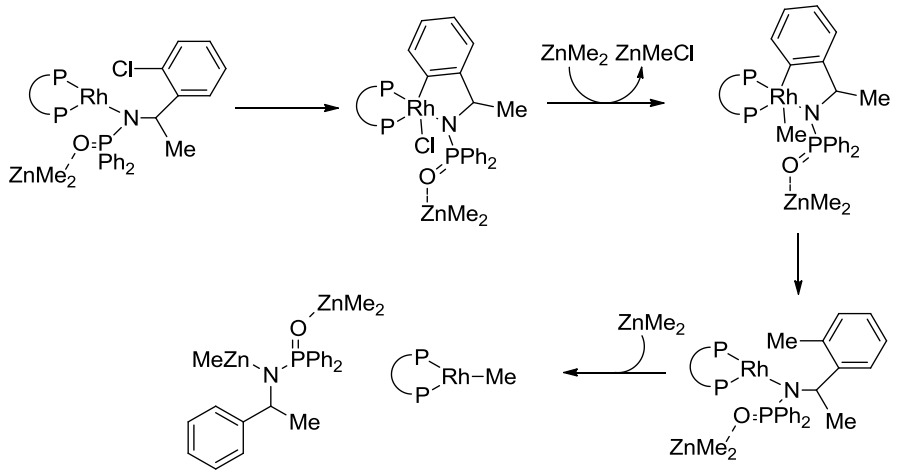
[a] Isolated yield; [b] from crude ^{1}H NMR spectrum; [c] determined by GC of acetamide or trifluoroacetamide derivative.

The reduction reaction is present in all cases. The results show that *ortho* substituents have a detrimental effect on the yield of the reaction (Entry 9). The enantiomeric excess is best in the case of the unsubstituted phenyl at 93%. When the reaction was run using 2-chloro imine **2.20k** as the starting material, there appeared to be rotamers present in the ^{1}H NMR spectrum. However, when the ^{1}H NMR spectrum was run at an elevated temperature (70 °C) no change

in ratio was observed. Further analysis of the ^{1}H NMR spectrum showed a peak at 2.04 ppm this lead us to deduce that the *ortho*-chlorine had be replaced by a methyl in ~50% of the product (Scheme 47). This was confirmed by the comparison with an independently prepared sample of the 2-methyl product **2.21i**. This could be explained mechanistically by the insertion of rhodium into the carbon-chlorine bond (Scheme 48). Transmetallation with dimethylzinc followed by reductive elimination would lead to the *ortho* methyl compound.



Scheme 47



Scheme 48

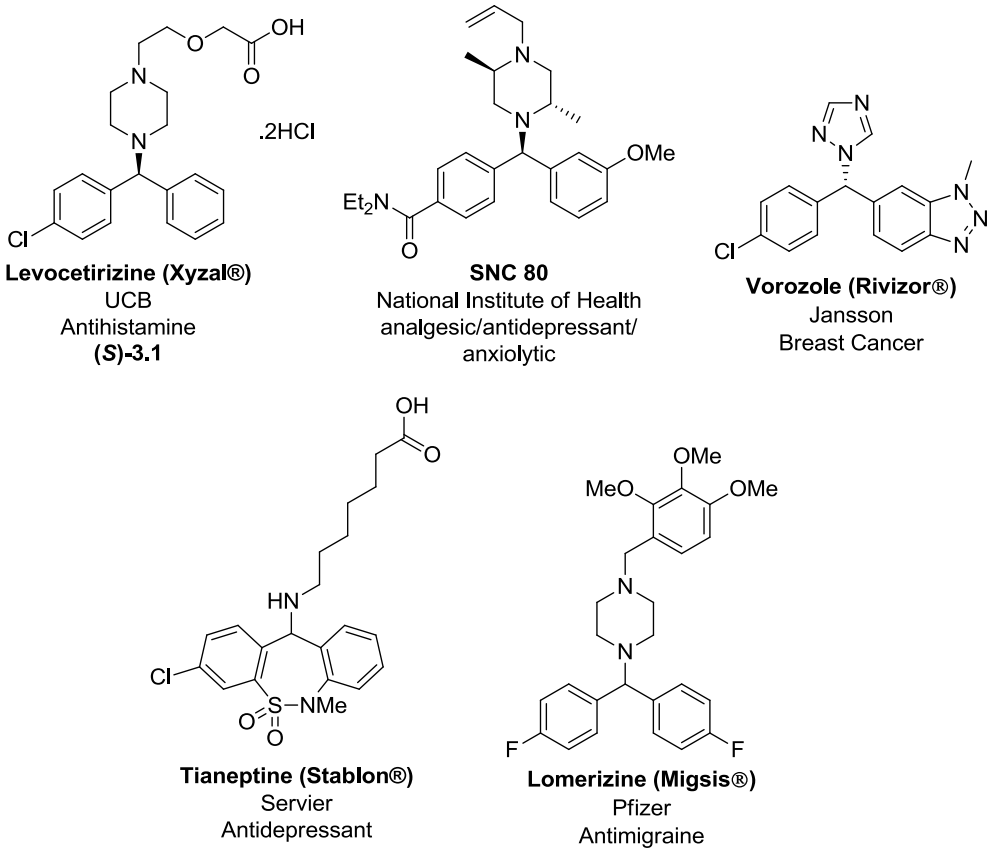
In conclusion, conditions have been found that allow for methyl addition to the activated *N*,*N*-diphenylphosphinoyl imines **2.20** in moderate to good yields and good to excellent enantiomeric excesses. Complications were observed due to competing chemoselectivity (reduction) issues. Fortunately, the phosphinamides **2.21** are all crystalline compounds and further enantioselective enrichment can be achieved through simple recrystallisation.

The aim from here was to investigate a new protecting group rather than the high molecular weight *N*,*N*-diphenylphosphinoyl group and the look at the addition of other groups, in particular aryl groups.

Chapter 3

3.1 Chiral Diarylmethylamines

Chiral diarylmethylamines are valuable chemical motifs occurring in pharmaceutical targets as can be seen in Scheme 49. Cetirizine (Zyrtec®) is a second-generation, non-sedating, antihistamine drug,[117] the levo enantiomer (*S*)-Cetirizine dihydrochloride (Xyzal®, **(*S*)-3.1**) (Scheme 49) was found to have a two-fold higher affinity for H_1 receptors than the racemic Cetirizine.[118] Asymmetric synthesis and administration of the eutomer **(*S*)-3.1** is therefore, a much more efficient strategy than using the racemate, Cetirizine **(±)-3.1**.



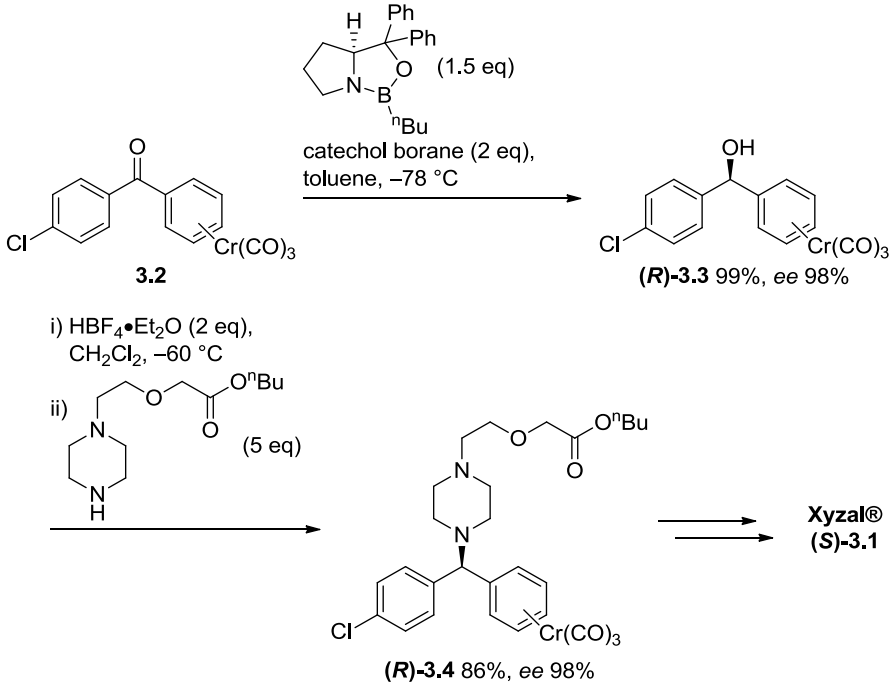
Scheme 49

Further biologically active diarylmethylamine containing molecules include: non-peptidal δ-receptor agonists[119-121] for example SNC 80; Tianeptine an antidepressant;[122] Lomerizine a calcium channel blocker used for the treatment of migraines;[123] Vorozole for the treatment of breast cancer,[124] a series of Thromboxane A2 receptor agonists[125] amongst others.[126-129] Some of these are limited to symmetrical diarylmethylamines (for example Lomerizine,

Scheme 49), possibly due to the lack of commercially available chiral diarylmethylamines and limitations to their synthesis on scale. Diarylmethylamines have also been used as protecting groups for example in the synthesis of carbapenem intermediates by Ito's group[130] and in the preparation of α-arylglycines by Petasis' group.[131]

3.1.1 Synthesis of Levocetirizine

Routes to levocetirizine **(*S*)-3.1** based on resolution of 4-chlorobenzhydrylamine with (+)-tartaric acid[132] and preparative chiral HPLC of an amide derivative[133] have been reported. The first enantioselective synthesis was reported by Corey *et al.* in 1996[134] using a Corey-Bakshi-Shibata (CBS) reduction of 4-[η^6-chromium tricarbonylbenzoyl]chlorobenzene **3.2** to give the enantioenriched alcohol **3.3** (Scheme 50). Introduction of the piperazine unit proceeded with complete retention of configuration due to the stability of the chromium stabilised carbocation.[135] The synthesis of Xyzal® **(*S*)-3.1** was completed in a further two steps. Other approaches to levocetirizine **(*S*)-3.1** have been based on asymmetric additions of organometallic nucleophiles to activated imines. As this type of reaction is central to this Thesis, such approaches will be discussed in more detail in the next section.



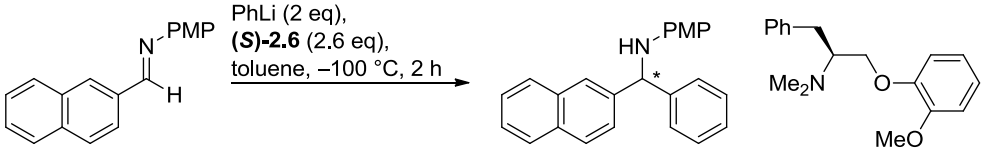
Scheme 50

3.2 Additions to Activated Aldimines

Investigations into the arylations of imines have lagged behind that into the arylation of aldehydes.[136,137] This is due to the inherent lower electrophilicity of imines, the risk of hydrolysis under the arylation conditions and the need for an activating group that can then be removed from the amine addition product. The current state of the literature up to 2012 for arylation of activated aldimines will now be surveyed, looking at each type of nucleophile in turn.

3.2.1 Aryllithium Reagents

Aryllithium reagents are both highly nucleophilic and basic species, which limits the range of functional groups that can be present in the substrates they are reacted with. Aryllithium reagents can be made by lithium-halogen exchange from the appropriate aromatic halide; only phenyllithium is commercially available. Aryllithium reagents can be added to achiral imines in the presence of enantiopure chiral ligands. This approach relies on the ligand-aryllithium complex being more reactive than the uncoordinated aryllithium reagent, so low temperatures are employed to minimise the background reaction. Tomioka *et al.*[62] reported the first example in 1990 using a stoichiometric amount of an enantiopure amino-ether ligand **(*S*)-2.6** in the addition of phenyllithium to *p*-methoxyphenylimine **3.4** to give the enantioenriched addition product **3.5** (the absolute stereochemistry was not defined) (Scheme 51). A further example from the Tomioka group using a bulkier 4-methoxynaphthyl protecting group gave an excellent enantiomeric excess of 92%.[69]

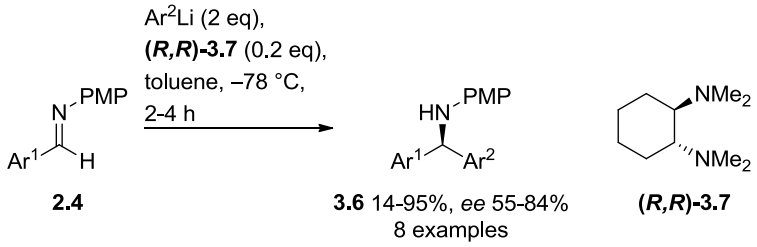


3.4 **3.5** 86%, *ee* 74% **(*S*)-2.6**

Scheme 51

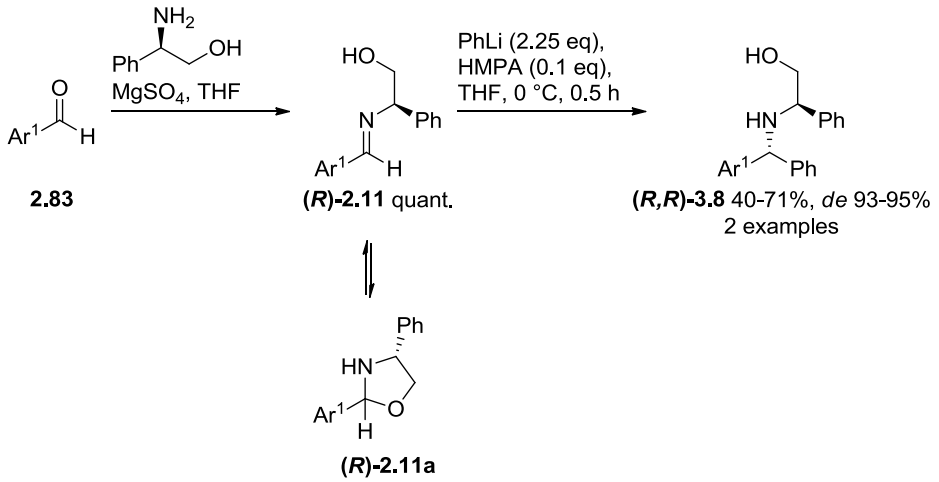
Later the group of Alexakis reported 1,2-diamine ligand **(*R,R*)-3.7** that could be used in substoichiometric quantities to give addition product **3.6** (Scheme 52).[138,139] However, consistently higher yields were achieved when stoichiometric ligand loadings were used. The

p-methoxyphenyl protecting group can be removed by reduction with ammonium cerium(IV) nitrate (CAN).



Scheme 52

Alternatively, an aryllithium reagent can be added to an imine bearing an enantiopure chiral activating group. Delorme and co-workers[140] reported the diastereoselective addition of phenyllithium to imines **(*R*)-2.11** (in equilibrium with oxalidinone **(*R*)-2.11a**) derived from an aryl aldehyde and (*R*)-phenylglycinol (Scheme 53). The auxiliary could be removed by treatment with lead tetraacetate to give the free amine in 60% yield.

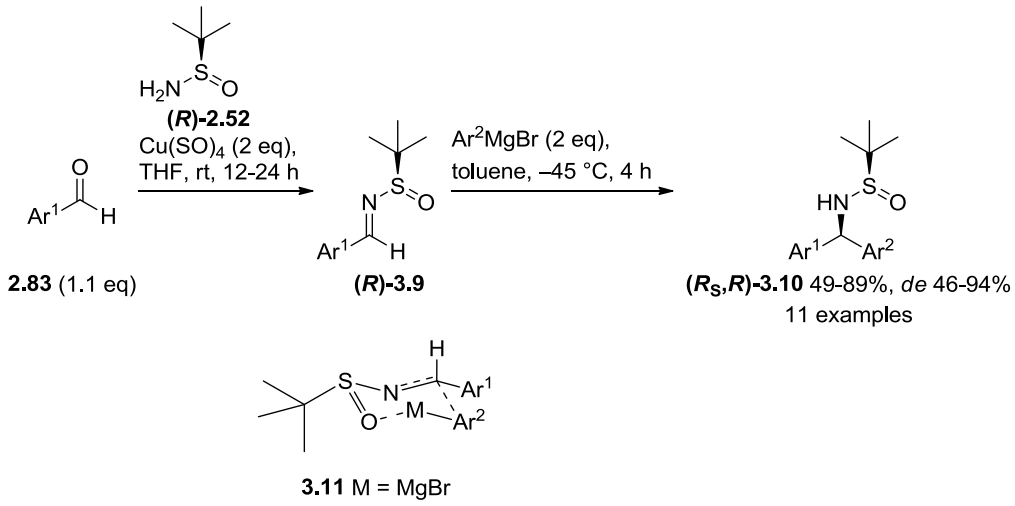


Scheme 53

3.2.2 Aryl Grignard Reagents

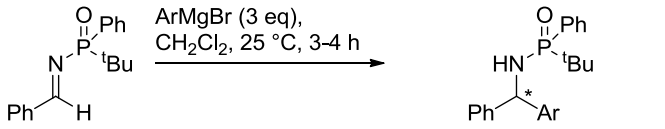
Aryl Grignard reagents are highly nucleophilic and basic species, similar to aryllithium reagents, which limits the range of functional groups that can be present in the substrates they are reacted with. Aryl Grignard reagents can be synthesised from the appropriate aryl bromide and magnesium turnings; there are more examples of commercially available aryl Grignard reagents than aryllithium reagents.

Ellman has developed a chiral auxiliary approach using enantiopure *N*-*tert*-butanesulfinyl imines (Scheme 54).[141] The sulfinyl group both increases the electrophilicity of the imine and promotes diastereofacial selectivity. The chiral auxiliary **(*R*)-2.52** can be made in two steps from di-*tert*-butyl disulfide in 65% overall yield and >99% *ee*[142] and both enantiomers are now commercially available. The imine **(*R*)-3.19** is then made by condensation with the aldehyde in the presence of a Lewis acid, typically $CuSO_4$ (Scheme 54).[143] Addition of Grignard reagents to these imines proceeds with high diastereoselectivity *via* a proposed six-membered ring transition state **3.11** with magnesium chelating the oxygen of the sulfinyl group,[141] non-coordinating solvents are found to give the highest diastereoselectivities as the transition state is not disturbed. Plobeck *et al.*[144] prepared diarylmethylamines **(R_S,*R*)-3.10** in generally good yields and diastereomeric ratio using this method (Scheme 54). They found using aryllithium reagents gave a switch in diastereoselectivity, as the six-membered ring transition state is not formed. This approach has also been applied to the synthesis of levocetirizine **(*S*)-3.1**.[145]



Scheme 54

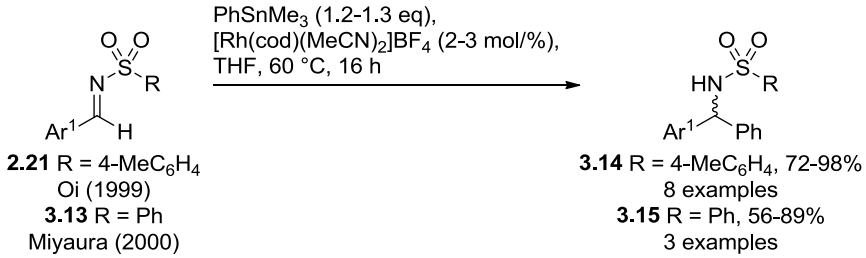
The free amine can be isolated using mild acidic conditions[146] and the chiral auxiliary can be recycled.[147] Colobert *et al.*[20,74] have developed a *P*-chirogenic *N*-phosphinoylimine **(±)-2.18** (Scheme 55) and have achieved some encouraging diastereoselectivity with the addition of aryl Grignard reagents, however, only racemic imine has been used so far.



Scheme 55

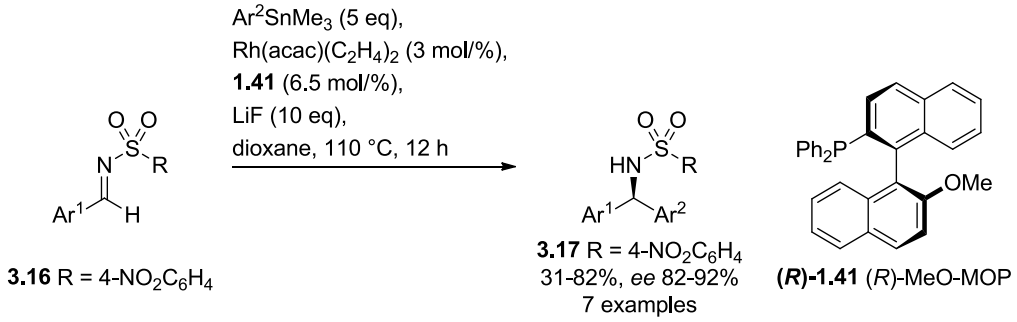
3.2.3 Aryl Stannanes

Stannane nucleophiles are much less nucleophilic than aryllithium and aryl Grignard reagents and typically a catalyst will be need to be employed with them. However, the low nucleophilicity and basicity of these species is an advantage as it increases the range of functional groups that can be tolerated in the reaction. A disadvantage of stannane reagents is their high toxicity. Some tributylaryl stannanes and fewer trimethylaryl stannanes are commercially available. Trimethylaryl stannanes are made from the appropriate aryl Grignard reagent and trimethyl tin bromide.



Scheme 56

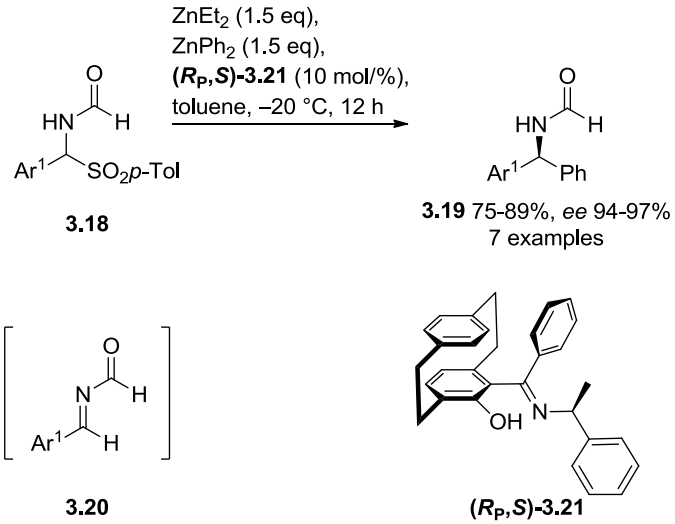
The groups of Miyaura[148] and Oi[149,150] reported the first examples of transition metal catalysed additions to aldimines **2.21** and **3.13** using trimethylphenyl stannane as the nucleophile and a cationic rhodium complex as complex (Scheme 56). The addition of phosphine ligands was detrimental to the reaction.



Scheme 57

The first example of an asymmetric transition metal catalysed synthesis of diarylmethylamines was reported by Hayashi *et al.* in 2000 (Scheme 57).[151] Aryl stannanes were added to *N*-alkylidenesulfonamides **3.16** using a neutral rhodium catalyst and an enantiopure chiral monodentate phosphine ligand **(*R*)-1.41**. The highest enantioselectivity was achieved with a nosyl protecting group. The use of five equivalents of toxic stannane reagents has led to the pursuit of other nucleophiles.

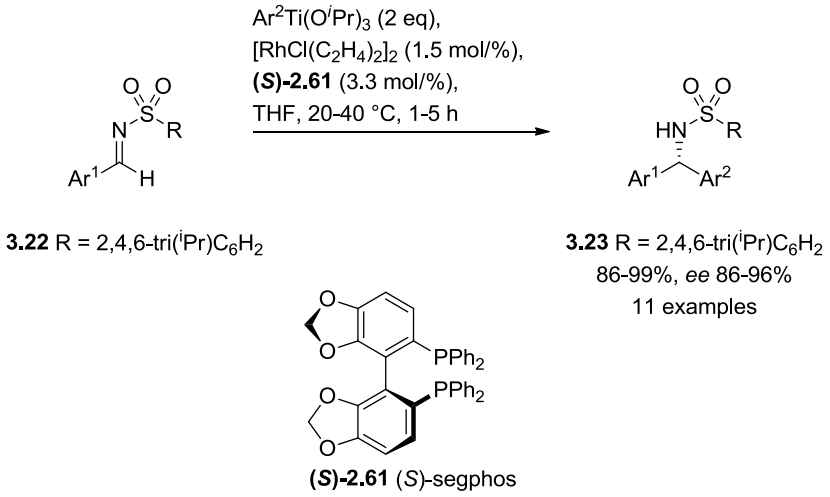
3.2.4 Arylzinc Reagents



Scheme 58

Following their success with the enantioselective addition of diphenylzinc to aldehydes, Bräse *et al.* studied phenyl transfer to *N*-formyl imines **3.20** (Scheme 58).[152] A mixed diorganozinc species was formed *in situ* from diphenylzinc and diethylzinc. Mixed diorganozinc reagents are less reactive than diarylzincs, which presumably lowers the background reaction. The *N*-formyl imines **3.20** were formed *in situ* from the sulfinate adduct **3.18**. The [2.2]paracyclophane-based ketimine ligand **(R_P,*S*)-3.21** shown in Scheme 58 was found to give the best enantioselectivities with no ethylation product observed. The *N*-formylamines **3.19** can be deprotected by acidic methanolysis with no racemisation. A limitation of this approach is that substitution can only be introduced on the aryl group of the imine, as no substituted diarylzinc reagents are available.

3.2.5 Aryl Titanium Reagents



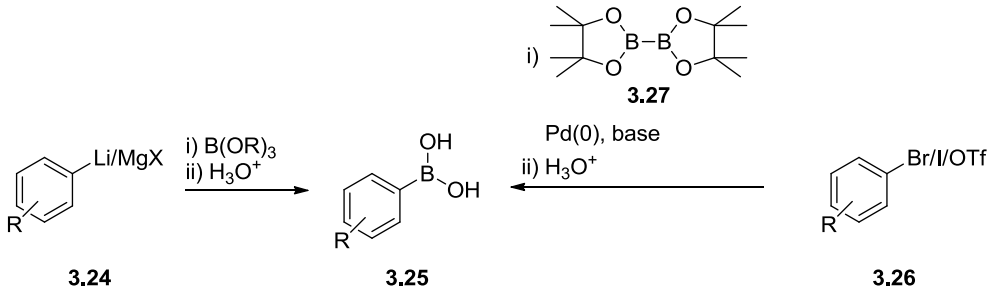
Scheme 59

Hayashi *et al.* found aryl titanium reagents can undergo transmetallation with rhodium complexes and give addition products imines.[153] The titanium reagents were prepared from the appropriate aryllithium and chlorotriisopropoxytitanium.[154] The optimised conditions used the imine activated with a bulky 2,4,6-triisopropylbenzenesulfonyl group **3.22** and (*S*)-segphos **(*S*)-2.61** (Scheme 59). The protecting group can be removed from the resulting amine **3.23** using the usual methods for tosyl deprotection (SmI_2 in HMPA/THF, $Li/NH_{3(liq)}$ in THF or RedAl in toluene).

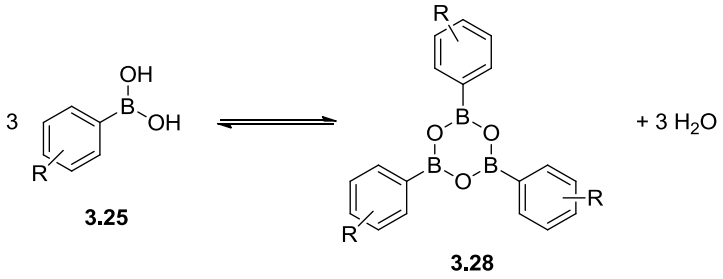
3.2.6 Aryl Boron Reagents

Organoboron sp^2-nucleophiles have the advantage of often being stable to air, oxygen and moisture, compatible with a wide range of functional groups and give non-toxic by-products.[28,155] No special handling techniques are needed and they are only weakly nucleophilic so many functional groups can be tolerated. The success of the Suzuki-Miyaura cross-coupling has lead to the commercial availability of many substituted aryl boronic acids. Aryl boronic acids can be synthesised from aryl Grignard/lithium reagents **3.24** and trialkyl borates followed by hydrolysis of the intermediate boronic ester or by palladium catalysed cross-coupling of aryl halides or triflates **3.26** with the expensive diborylpinacolate **3.27** which

is commercially available and allows more sensitive functional groups to be present (Scheme 60).[155]



Scheme 60

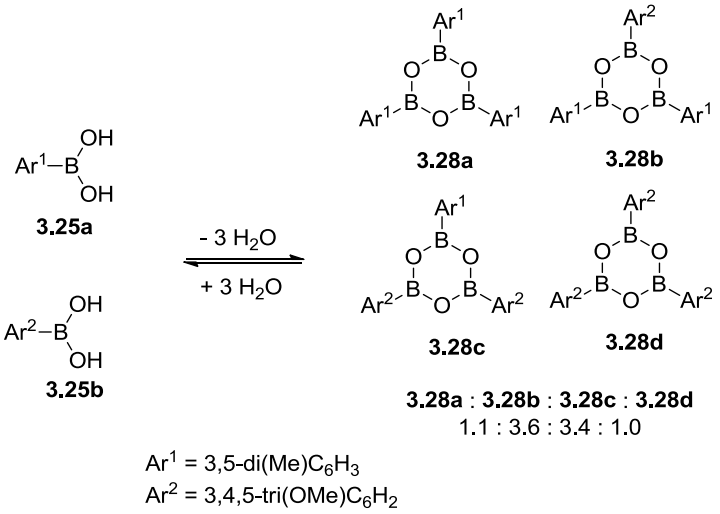


Scheme 61

Boroxines **3.28** (also called boronic acid anhydrides) are dehydrated boronic acids. Although boroxine formation is entropically favoured due to the formation of three equivalents of water, boronic acids tend to exist as mixture of the boronic acid and anhydride, and in solution the two species are in equilibrium (Scheme 61).[156] Boroxines are isoelectronic with benzene, however, they not considered aromatic heterocycles.[157-160] They are known to readily form Lewis acid-base adducts with amines typically 1:1 boroxine:amine.[161,162] Aryl boronic acids bearing electron-donating groups form boroxines with increased stability whilst electron-withdrawing groups and *ortho*-substituents destabilise the boroxine and accelerate their hydrolysis.[156,161] Boroxines have a C_3-symmetric planar structure in the solid state (as shown by X-ray crystallography), with some exceptions e.g. *ortho*-methyl which has a propeller like structure with the phenyl rings twisted out of plane. Boroxines have applications in materials chemistry such as flame retardants and lithium ion battery anion acceptors.[163]

The group of Tokunaga[164] studied the formation of hetero-aryl boroxines from a mixture of two boronic acids using ^{1}H NMR spectroscopy to calculate the equilibrium constants in solution. Scheme 62 shows the experimental distribution of boroxines was found

to be close to the statistical distribution of 1:3:3:1. However, no attempt was made to separate the boroxines.

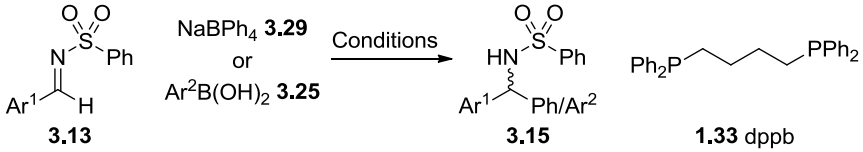


Scheme 62

3.2.6.1 Rhodium Catalysis

The first transition-metal catalysed addition of an aryl boron nucleophile to an activated imine was reported by the group of Miyaura in 2000 (Entry 1, Table 19).[148] Using sodium tetraphenylborate **3.29** as the aryl source and a cationic rhodium complex with a phosphine ligand **1.33** gave addition product **3.15** in good yield. However, there are few commercially available functionalised sodium tetraarylborates and 5.2 equivalents of the aryl group with respect to the imine are required.

Table 19



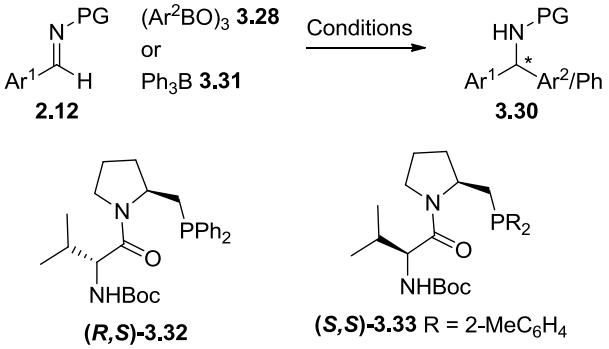
Entry	Boron Species	Conditions	**3.15** [%]
1	**3.29** (1.3 eq)	$[Rh(cod)(MeCN)_2]BF_4$ (3 mol/%), **1.33** (3 mol/%), dioxane, 90 °C, 3-16 h	68-94 6 examples[148]
2	**3.25** (2 eq)	$[Rh(cod)(MeCN)_2]BF_4$ (3 mol/%), dioxane, 95 °C, 16 h	68-99 8 examples[165]

Later the same year, Miyaura *et al.*[165] reported the first catalysed addition of aryl boronic acids (and esters) using similar conditions (Entry 2, Table 19). Many groups have since worked

on optimising an asymmetric, rhodium catalysed, boronic acid/boroxine arylation due to the utility of aryl boronic acid nucleophiles.

Tomioka and co-workers used a *N*-Boc-L-valine connected amidomonophosphane ligand **(*R,S*)-3.32** with a rhodium(I) catalyst to arylate *N*-tosylimines with aryl boroxines **3.28** (Entry 1, Table 20).[166] The highest enantioselectivities were reported with imines bearing an *ortho*-trimethylsilyl group, which could then be replaced by a proton or halogen. Later steric tuning of the ligand allowed arylation of *N*-diphenylphosphinoyl aldimines with higher enantiomeric excess and the advantage of a milder deprotection (Entry 2, Table 20) although higher catalyst loadings and longer reaction times were needed.[167] In an attempt to limit imine hydrolysis the group of Tomioka have recently reported the use of triphenylborane **3.31** as the aryl source in an anhydrous reaction system (Entry 3, Table 20).[168,169]

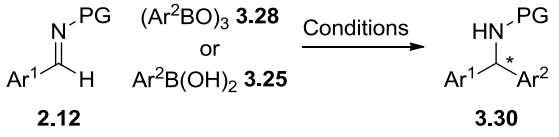
Table 20

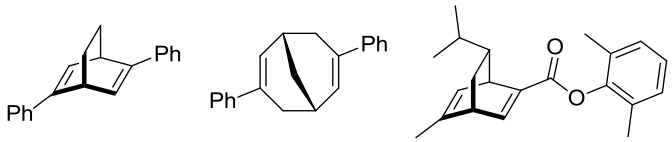


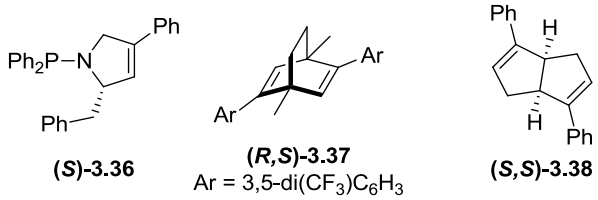
Entry	PG	Conditions	**3.41** [%]	*ee* [%]
1	Ts	**3.28** (1.7 eq), $Rh(acac)(C_2H_4)_2$ (3 mol/%), **(*R,S*)-3.32** (3.3 mol/%), ^{n}PrOH, 60-100 °C, 1-3 h	83-99 11 examples	66-94 (*R*)[166]
2	$P(O)Ph_2$	**3.28** (1.7 eq), $Rh(acac)(C_2H_4)_2$ (6 mol/%), **(*S,S*)-3.33** (6.6 mol/%), 4 Å M.S., dioxane/^{n}PrOH, 80 °C, 12 h	76-96 14 examples	86-99 (*S*)[167]
3	$P(O)Ph_2$	**3.31** (1.7 eq), $Rh(acac)(C_2H_4)_2$ (6 mol/%), **(*S,S*)-3.33** (6.6 mol/%), KF/Celite (2 eq), ^{t}BuOH, 100 °C, 1-12 h	84-94 8 examples	90-96 (*S*)[168-169]

A series of cyclic chiral diene ligands have been developed in the Hayashi group and have been applied to the arylation of both *N*-tosyl- and *N*-nosylarylimines. Chiral diene ligands will be discussed in more detail in Section 3.2.7. The addition of aryl boroxines **3.28** to *N*-tosylarylimines using $[RhCl(C_2H_4)_2]_2$ and (*R,R*)-Ph-bod **(*R,R*)-2.39** (Entry 1, Table 21) resulted in high yield and enantioselectivities.[170]

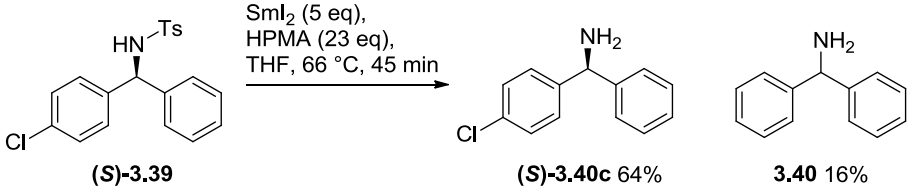
Table 21







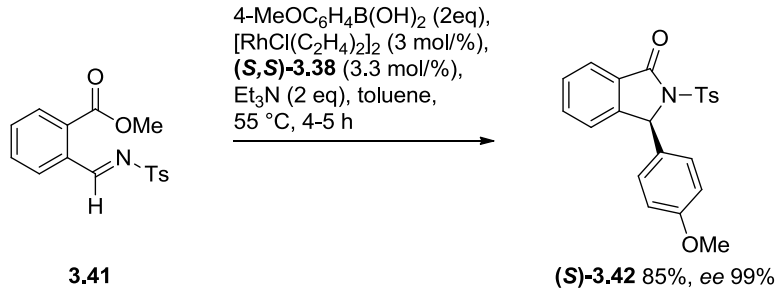
Entry	PG	Conditions	**3.30** [%]	*ee* [%]
1	Ts	**3.28** (1.2 eq), $[RhCl(C_2H_4)_2]_2$ (3 mol/%), **(*R,R*)-2.39** (3.3 mol/%), $KOH_{(aq)}$ (20 mol/%), dioxane, 60 °C, 6 h	94-99 11 examples	92-99 (*R*)[170]
2	Ns	**3.28** (1.2 eq), $[RhCl(\mathbf{(R,R)\text{-}3.34})]_2$ (3 mol/%), $KOH_{(aq)}$ (20 mol/%), dioxane, 60 °C, 6 h	94-99 12 examples	95-99 (*R*)[171]
3	Ns	**3.28** (0.67 eq), $[RhCl(C_2H_4)_2]_2$ (0.3 mol/%), **(*R,R*)-3.35** (0.33 mol/%), $KOH_{(aq)}$ (20 mol/%), dioxane, 60 °C, 6 h	90-98 10 examples	97->99 (*R*)[172]
4	Ts	**3.28** (1 eq), $[RhCl(\mathbf{(S)\text{-}3.36})]_2$ (2.5 mol/%), KOH (2 eq), dioxane:H_2O 50:1, 60 °C, 6 h	70-95 13 examples	89-98 (*S*)[173]
5	Ts	**3.28** (2 eq), $[RhCl(C_2H_4)_2]_2$ (0.75 mol/%), **(*R,S*)-3.37** (1.65 mol/%), KOH (2 mol/%), MeOH/CH_2Cl_2 (10:1), rt, 3h	91	94[174]
6	Ts	**3.25** (2 eq), $[RhCl(C_2H_4)_2]$ (3 mol/%), **(*S,S*)-3.38** (3.3 mol/%), Et_3N (2 eq), toluene, 55 °C, 4-5 h	56-99 20 examples	98-99 (*R*)[175]



Scheme 63

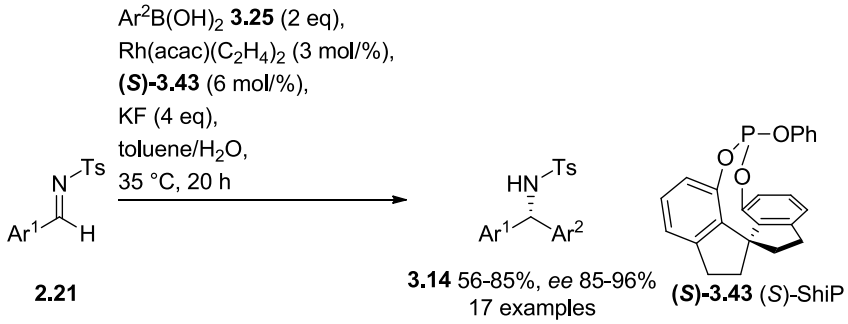
However, deprotection of the tosyl protected amine **(*S*)-3.39** using SmI_2 in HMPA/THF lead to partial dechlorination of addition products bearing chlorine (Scheme 63).[170] The focus then moved to *N*-nosylarylimines, which can be deprotected under milder conditions (see Section

1.2). The (*R,R*)-Ph-bnd ligand **(*R,R*)-3.34** was more effective than (*R,R*)-Ph-bod **(*R,R*)-2.39** with *N*-nosylarylimines (Entry 2).[171] A bicyclo[2.2.2]octadiene ligand **(*R,R*)-3.35** was developed with a simpler synthesis than previous dienes and also was effective in arylation of *N*-nosylarylimines (Entry 3).[172] The Hayashi group have also developed a bidentate phosphine-olefin ligand **(*S*)-3.36** which was successfully used in the addition of aryl boroxines to *N*-tosylimines (Entry 4).[173] Another chiral diene ligand **(*R,S*)-3.37** designed by the group of Carnell has been used to give product **3.30** in good yield and enantioselectivity (Entry 5).[174] Lin *et al.* designed a tetrahydropentalene ligand **(*S,S*)-3.38** with which boronic acids rather than boroxines were effective arylating agents (Entry 6).[175] When an imine bearing an *ortho*-ester group **3.41** was used, lactamisation occurred under the reaction conditions to give a chiral isoindolinone **(*S*)-3.42** (Scheme 64), however, deprotection was not reported.



3.41 **(*S*)-3.42** 85%, *ee* 99%

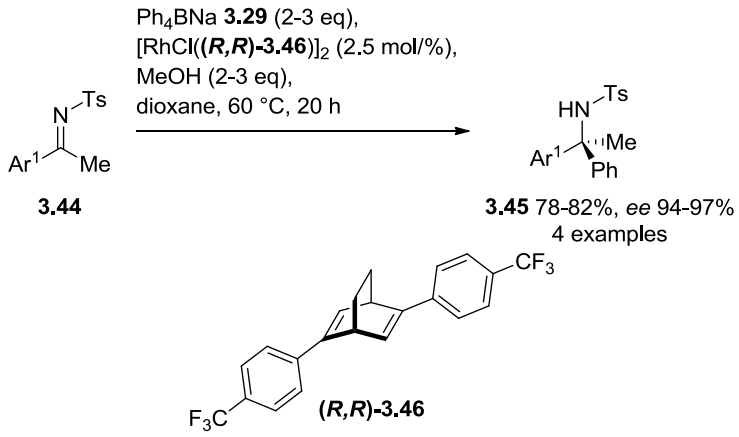
Scheme 64



2.21 **3.14** 56-85%, *ee* 85-96% 17 examples **(*S*)-3.43** (*S*)-ShiP

Scheme 65

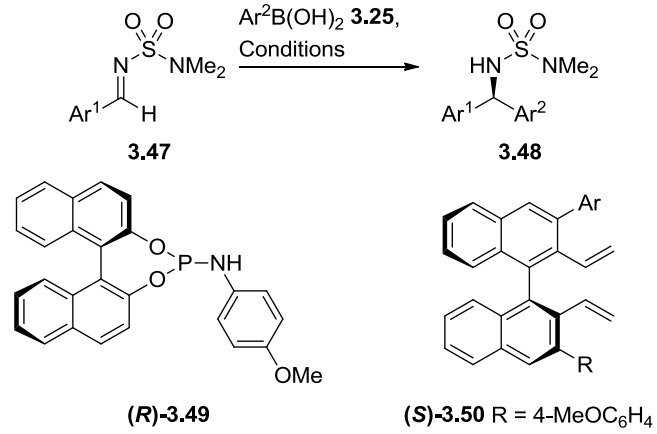
Zhou *et al.* reported a spiro-monophosphite ligand **(*S*)-3.43** used with a rhodium catalyst for the addition of boronic acids to *N*-tosylimines (Scheme 65).[176] Hayashi *et al.* have recently reported the use of diene ligand **(*R,R*)-3.46** (Scheme 66) for the rhodium catalysed aryl addition to *N*-tosylketimines **3.44**.[177] Although an undesirable aryl source is used in sodium tetraphenyl borate this is a rare example of the synthesis of enantiopure tertiary amines such as **3.45**.



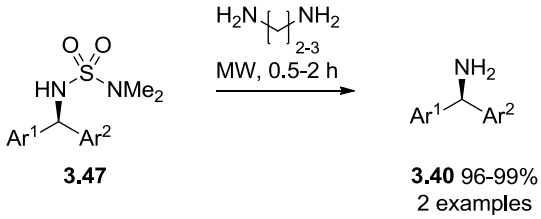
Scheme 66

Feringa and co-workers reported the low molecular weight *N*,*N*-dimethylsulfamoyl group as a protecting and activating group for the arylation of imines.[178] A rhodium/phosphoramidite **(*R*)-3.49** system achieved up to 94% *ee* of sulfamide **3.48** (Entry 1, Table 22). More recently Du *et al.* have used a novel acyclic binaphthyl-based chiral diene ligand **(*S*)-3.50** for the addition of boronic acids to these *N*,*N*-dimethylsulfamoylimines (Entry 2).[179] Deprotection to the free amine **3.40** could be achieved by transamination with 1,3-diaminopropane/ethylenediamine or in a microwave reactor without loss of enantiopurity (Scheme 67).

Table 22

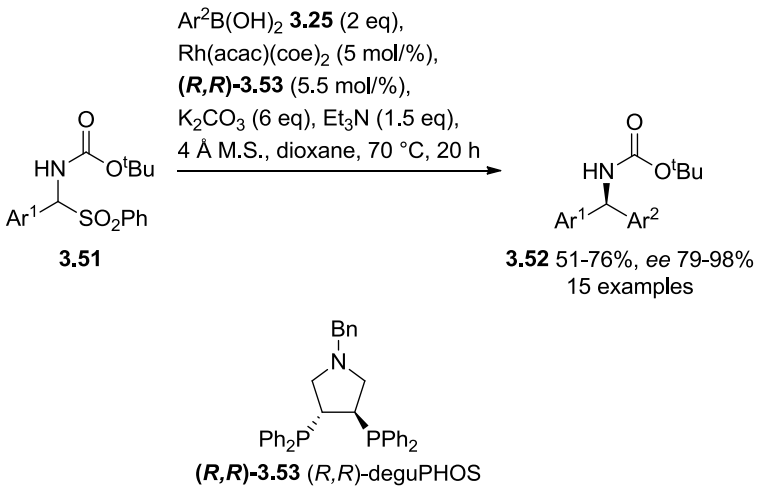


Entry	**3.25** [Eq]	Conditions	**3.48** [%]	*ee* [%]
1	1.3	$Rh(acac)(C_2H_4)_2$ (3 mol/%), **(*R*)-3.49** (7.5 mol/%), acetone, 40 °C, 4 h	72-97 10 examples	82-94[178]
2	2.0	$[RhCl(C_2H_4)_2]_2$ (2.5 mol/%), **(*S*)-3.50** (6.0 mol/%), Et_3N (2.0 eq), toluene, 30 °C, 4 h	48-82 10 examples	70-84[179]



3.47 **3.40** 96-99%
2 examples

Scheme 67

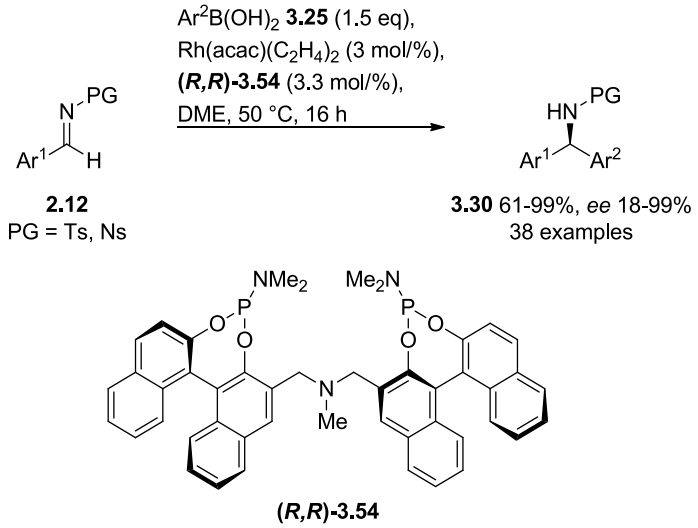


3.51 **3.52** 51-76%, *ee* 79-98%
15 examples

(*R,R*)-3.53 (*R,R*)-deguPHOS

Scheme 68

In addition to his work with chiral *N*-*tert*-butanesulfinimines, Ellman has also developed a rhodium catalysed aryl boronic acid addition to *N*-Boc-imine generated *in situ* from the sulfinate adduct **3.51** (Scheme 68).[180] Miyaura *et al.* have reported a rhodium catalysed aryl boronic acid addition using a novel *N*-linked bidentate phosphoramidite ligand **(*R,R*)-3.54** (Scheme 69).[181] They give 38 examples of aryl addition as well as chiral isoindolinone formation and synthesis of cryptostyline II.



2.12
PG = Ts, Ns

3.30 61-99%, *ee* 18-99%
38 examples

(*R,R*)-3.54

Scheme 69

Ellman also investigated the rhodium catalysed addition of boronic acids to enantioenriched *N-tert*-butanesulfinimines **(*R*)-3.9**.[182] High diastereoselectivities were achieved with a rhodium catalyst, *bis*-phosphine ligand **3.55** and slow addition of the boronic acid *via* a syringe pump (Entry 1, Table 23). Aliphatic aldimines were also compatible with this procedure. Batey *et al.* reported a similar system using triethylamine as an additive and no need for a phosphine ligand or slow boronic acid addition (Entry 2).[183]

Table 23

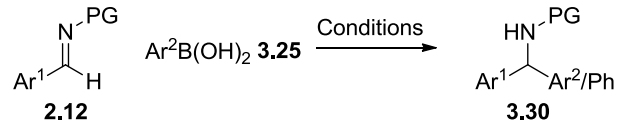
(*R*)-3.9 (*R*S,*S*)-3.10 **3.55** dppbenz

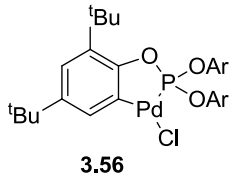
Entry	Conditions	(*R*S,*S*)-3.10 [%]	*de* [%]
1	$Rh(acac)(coe)_2$ (5 mol%), **3.55** (5.5 mol/%), dioxane, 70 °C, slow addition of boronic acid, 6-10 h	70-96 4 examples	92-98[182]
2	$[Rh(cod)(MeCN)_2]BF_4$ (5 mol/%), Et_3N (2 eq), dioxane/H_2O (1:2), rt, 2 h	47-quant. 13 examples	83-97[183]

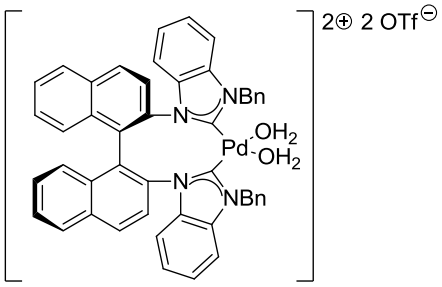
3.2.6.2 Palladium Catalysis

The addition of aryl boron nucleophiles to activated aldimines has also been attempted with palladium catalysis. In 2000 Hu *et al.* reported the use of phosphinite-based palladacycle **3.56** to give racemic **3.30** in good yield (Entry 1, Table 24).[184] Another set of conditions were developed by Ding (Entry 2).[185] An asymmetric example using the C_2-symmetric *N*-heterocyclic carbene palladium complex **3.57** with mild conditions which tolerates a range of functional groups has been reported by the group of Shi (Entry 3).[186]

Table 24



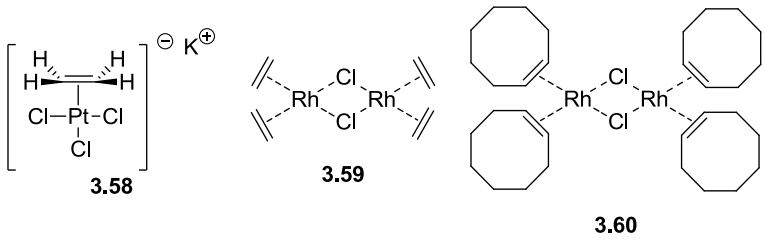




Entry	PG	Conditions	**3.30** [%]	*ee* [%]
1	Bs/Ts	**3.25** (2 eq), **3.56** (5 mol/%), K_3PO_4 (1 eq), toluene, rt, 24-48 h	63-90 9 examples[184]	n.a.
2	Ts	**3.25** (2 eq), $PdCl_2(PhCN)_2$ (5 mol/%), $^iPr_2NPPh_2$ (5 mol/%), K_2CO_3 (3 eq), 4 Å M.S., dioxane, 80 °C, 24 h	31-85 26 examples[185]	n.a.
3	Ts	**3.25** (2 eq), **(*R*)-3.57** (3 mol/%), $K_3PO_4.3H_2O$ (1 eq), 4 Å M.S., THF, 4 °C, 12-36 h	64-99 26 examples	60-94 (*R*)[186]

3.2.7 Diene Ligands

One of the first olefin complexes reported was Zeise's salt in 1827, a η^2-bonded ethylene and platinum complex **3.58** (Scheme 70).[187,188] Olefin complexes have been reported with Ni, Pd, Rh and Ir since then. Rhodium-olefin complexes **3.59** and **3.60** (Scheme 70) are commercially available and commonly used as precursors for chiral catalyst complexes. Yet only recently has the field of using chiral alkenes as ligands in asymmetric catalysis been investigated.



Scheme 70

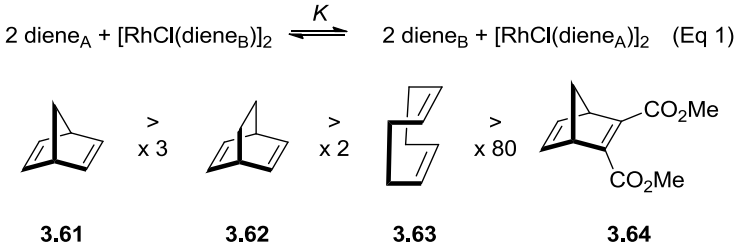
Traditionally chiral ligands chelate through phosphorus or nitrogen atoms with much stronger binding than alkenes. Precatalysts such as **3.59** and **3.60** are used and the alkenes are displaced by the chiral nitrogen or phosphorus ligands in solution. If the ligand exchange is incomplete,

the enantioselectivity may be reduced. Olefin ligands have the advantage of increased lability compared to nitrogen or phosphorus based ligands, which gives fast and quantitative exchange to the desired olefin complex. Olefin complexes have been found to catalyse some reactions faster than phosphine based ligands.[189]

The Dewar-Chatt-Duncanson model[190,191] for metal olefin binding describes a σ-bond formed by donation of a pair of electrons from the π-orbital of the double bond to a vacant *d* orbital on the metal centre (Scheme 71). This is complemented by a π back donation from a filled d orbital on the metal to the antibonding π* orbital of the alkene resulting in a rehybridisation of the carbon centres.

Scheme 71

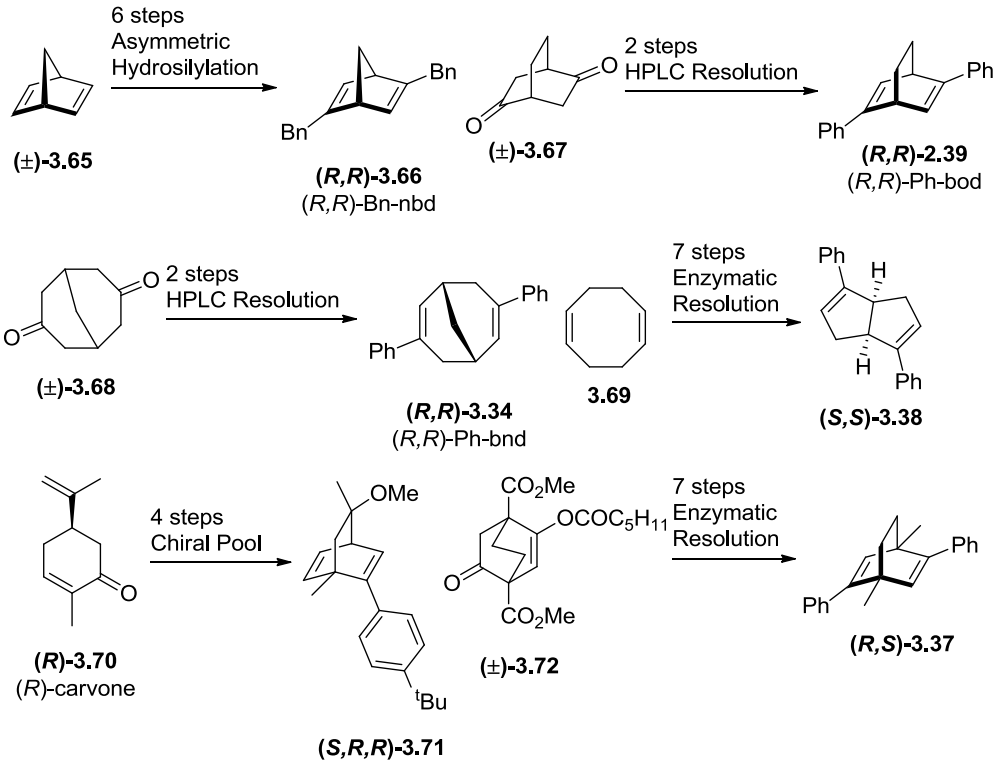
The amount of back donation increases with the principal quantum number of the metal centre, as the back donation increases there is increasing sp^3 character in the alkene carbon leading to a shift of around 1 ppm ^{1}H NMR spectra and 100-150 cm^{-1} in the IR spectra ($\upsilon_{C=C}$).[189] Electron-withdrawing groups on the alkene increase the amount of back-donation and increase the stability of the complex.



Scheme 72 Comparative increase of K for Equation 1.

Diene complexes are generally more stable than mono-olefin complexes due to the chelate effect. The relative stability of various diene ligands was investigated by Hogeveen *et al.* by studying the equilibrium constants of the ligand exchange (Equation 1, Scheme 72).[192] Bicyclo[2.2.1]hept-2,5-diene **3.61** was found to form some of the most stable complexes due to having an optimal bite angle and lack of steric hindrance or electron-donating groups around

the double bond. The rehybridisation of the carbon atoms that occurs on complexation also helps to reduce the ring strain of the carbocycle.



Scheme 73

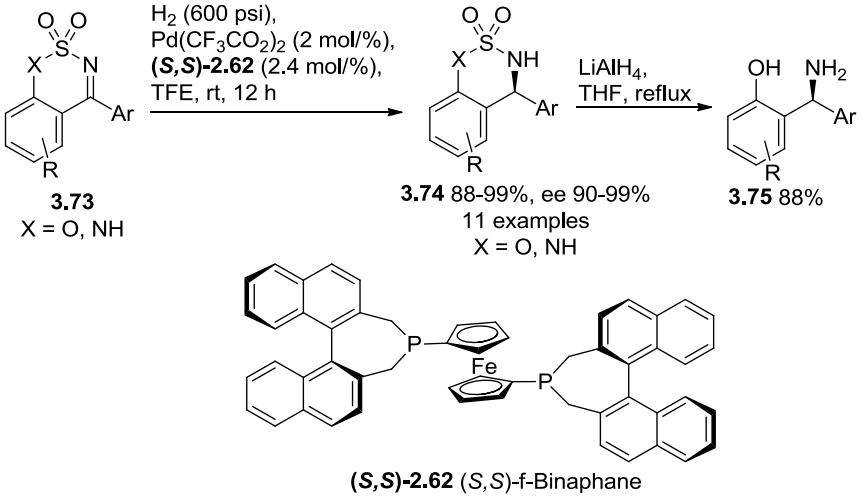
The Hayashi group have synthesised these ligands using asymmetric hydrosilylation (**(*R,R*)-3.66**)[193] or preparative HPLC (**(*R,R*)-2.39**, **(*R,R*)-3.34**)[170,171,194,195] to give the enantioenriched ligand (Scheme 73). Lin *et al.* used an enzymatic resolution of a diol intermediate to make ligand **(*S,S*)-3.38**.[175] Enzymatic resolution was also used to resolve racemic **(±)-3.72** (made from the commercially available dimer of dimethyl succinate) in the synthesis of **(*R,S*)-3.37** by Carnell *et al.*[174] Carreira used a readily available enantiopure starting material (*R*)-carvone **(*R*)-3.70** to make ligand **(*S,R,R*)-3.71**.[196] Recently phosphorus-olefin[173,197-201] and nitrogen-olefin[202] hybrid ligands have been developed by a number of groups.

3.3 Other Routes to Chiral Diarylmethylamines

Aryl additions to activated aldimines are not the only approach to chiral diarylmethylamines; the current literature of other synthetic routes will be reviewed in the following section.

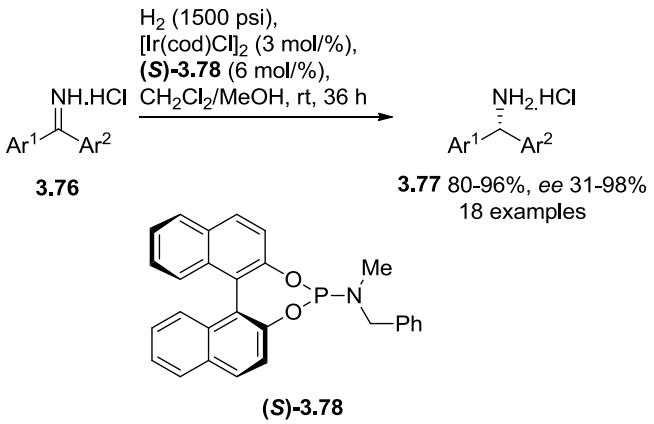
Resolution of diarylmethylamines is much less common than arylethanamines presumably due to the two substituents being of a similar steric bulk.

3.3.1 Reduction of Ketimines



Scheme 74

Asymmetric hydrogenation of cyclic activated imines **3.73** gave cyclic sulfamidates (X = O) and sulfamides (X = NH) **3.74** (Scheme 74).[203] The cyclic imines were prepared from *o*-hydroxybenzophenones or *o*-aminobenzophenones and sulfamoyl chloride (formed *in situ*). The cyclic sulfamidates (X = O) can be opened with lithium aluminium hydride to give amines **3.75**, this and the need for an *ortho*-hydroxy/amino group significantly limit the substrate scope.

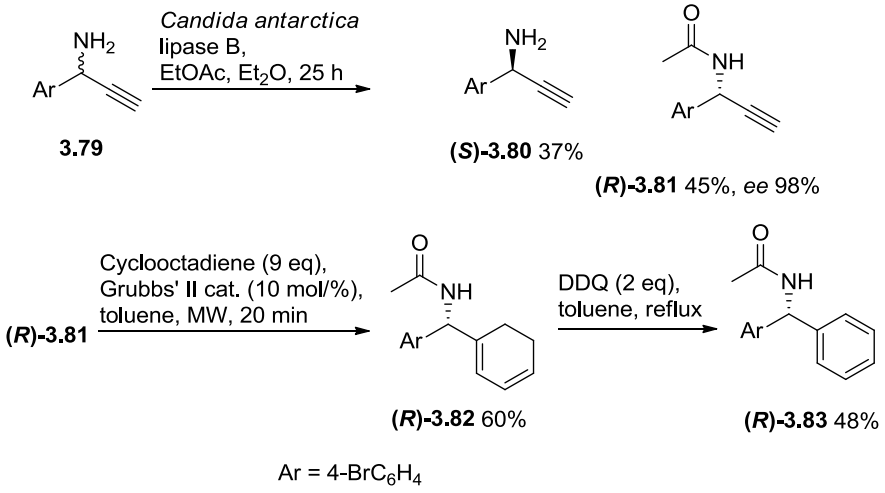


Scheme 75

The asymmetric hydrogenation of benzophenone imines **3.76** has been reported by the group of Gosselin.[99,204] The imines are prepared by Grignard reagent additions to benzonitriles. A

monodentate phosphoramidite ligand **(*S*)-3.78** with an iridium catalyst was found to give full conversion with a hydrogen pressure of 1500 psi (Scheme 75). The highest enantioselectivities (82-91%) were observed when an *ortho* substituent was present, compared to a *p*-methyl substituent (31%).

3.3.2 Other Routes



Scheme 76

The group of Botta devised a novel route to a chiral benzhydrylamine based on an enzymatic kinetic resolution of *N*-acetyl-1-aryl-1-propargylamine **3.79**.[205] The second ring was then built up using a methylene-free tandem metathesis[206] and oxidation with DDQ (Scheme 76).

3.4 Results and Discussion

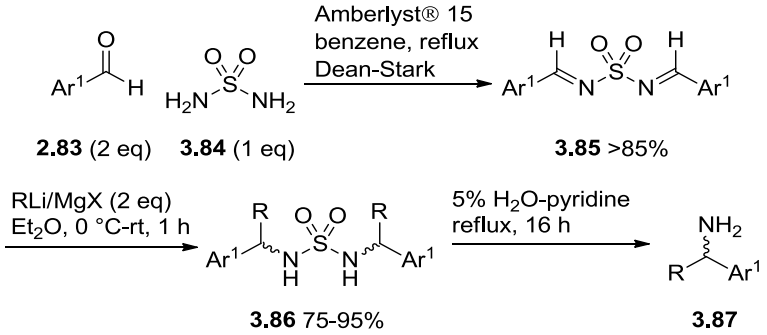
3.4.1 Aims and Objectives

As discussed in the introduction (Chapter 1), imines need electron withdrawing groups on the nitrogen to activate them towards nucleophilic addition. This group also must be easily removed, once the nucleophile has been added to give the free amine. The most commonly used protecting group in the aryl addition to imines is the tosyl group. However, the conditions to remove a tosyl group ($Li/NH_{3(liq)}$, Na/naphthalene) are incompatible with many functional groups, limiting the scope of diarylmethylamines accessible by this chemistry. It was our aim therefore, to use an activating group that could be removed under much milder conditions. We aimed to develop a catalytic asymmetric 1,2-addition of methyl or aryl nucleophiles to these

arylaldimines. The group used to activate the imine must be convenient to install from commercially available materials, have a low molecular weight, and be removed from the amine product using mild conditions that would be compatible with sensitive functionality. The ideal reaction would use readily available nucleophiles, ligands, and catalyst precursors. Once an addition protocol has been developed, the aim is to prove its utility by investigating the reaction's substrate scope.

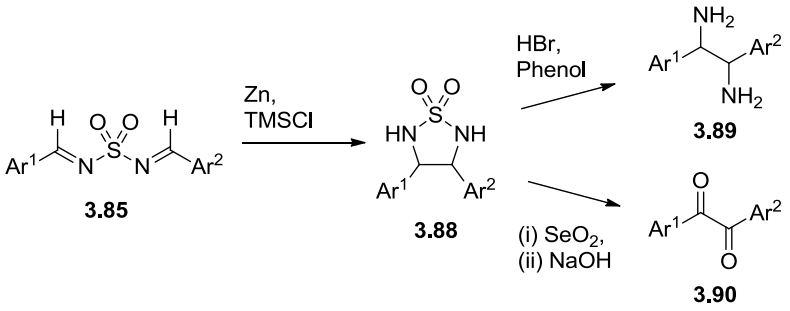
3.4.2 *Bis*-Sulfamyl Imines

In 1986 Davis *et al.* reported the synthesis of a new class of imines **3.85** from the condensation of aryl aldehydes and sulfamide (Scheme 77).[207] Grignard and organolithium reagents could be added to these imines to give sulfamides **3.86** and then the sulfamide linker cleaved to give two molecules of the beta-branched amine **3.87**. The deprotection occurred under very mild conditions using 5% H_2O-pyridine.



Scheme 77

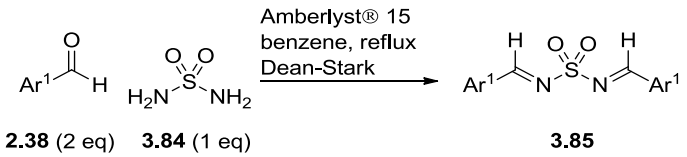
From our perspective, however, this looked an attractive substrate for rhodium-catalysed aryl addition and no asymmetric additions to this substrate have been reported. Since this was reported relatively few groups have made use of this route to secondary amines.[208] Pansare *et al.* have used these imines as substrates for an intramolecular reductive cross-coupling with zinc (Scheme 78) to make vicinal diamines **3.89**[209] and diketones **3.90**.[210]



Scheme 78

The condensation of benzaldehyde **2.83a** and sulfamide following the procedure of Davis[207] gave the *bis*-sulfamyl imine **3.85a** in good yield as a crystalline solid (Table 25), following this success a range of imines **3.85** were prepared. Unfortunately, some of the desired imines could not be isolated cleanly due to their insolubility. For example, in the condensation of 4-(trifluoromethyl)benzaldehyde with sulfamide, a mixture of mono- and *bis*-sulfamyl imines crashed out of the reaction mixture and then could not be separated by recrystallisation.

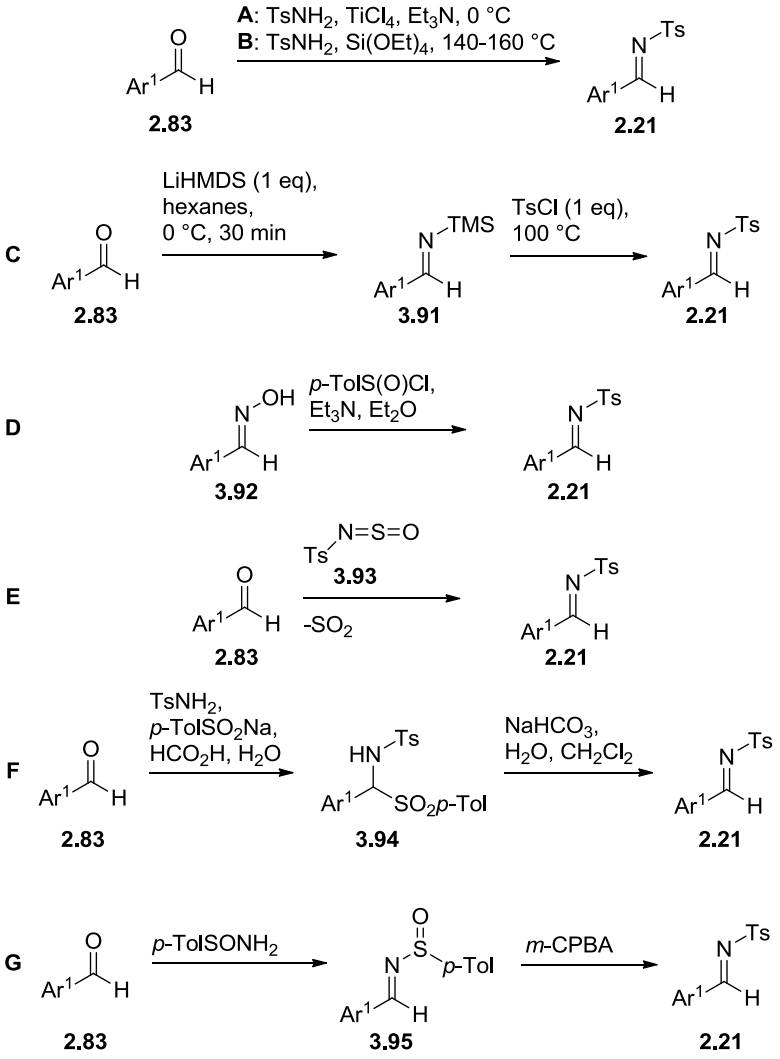
Table 25



Entry	Ar^1	Imine	**3.85** [%]
1	Ph	**3.85a**	66
2	4-FC_6H_4	**3.85b**	77
3	4-MeC_6H_4	**3.85d**	57
4	2-MeC_6H_4	**3.85e**	45
5	4-$MeOC_6H_4$	**3.85f**	71
6	3-MeC_6H_4	**3.85h**	72
7	4-BrC_6H_4	**3.85i**	43

For comparison, methods for making *N*-tosyl imines **2.21** will be reviewed briefly. *N*-Tosyl imines **2.21** can be prepared from the amine and non-enolisable aldehydes using the titanium tetrachloride procedure of Jennings *et al.* (Scheme 79, Route **A**).[110,111] A milder Lewis acid

approach (Route **B**) was developed by Love *et al.* using tetraethyl orthosilicate.[211,212] Or also by use of an ion exchange resin and azeotropic removal of water as seen in Scheme 77.[213] Georg *et al.* described a two-step procedure *via* the reaction of *N*-(trimethylsilyl) imine **3.91** with tosyl chloride (Route **C**).[214]



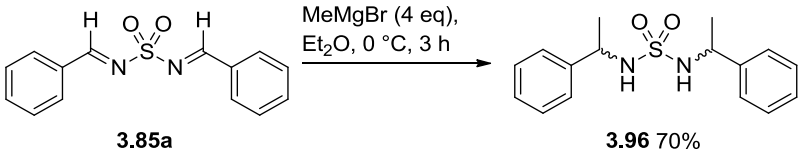
Scheme 79

The Hudson reaction (Route **D**), forms *N*-tosyl imines **2.21** by treatment of oximes **3.92** with a sulfinyl chloride[215-217] or sulfinyl cyanide[218] to give an intermediate which undergoes a radical rearrangement (an analogous route to *N*-diphenylphosphoryl imines was described in Section 2.1). The Kresze reaction (Route **E**) proceeds by [2+2]-cycloaddition of an aldehyde with *N*-sulfinyl sulfonamides (prepared from a sulfonamide and thionyl chloride) to give an intermediate which eliminates sulphur dioxide to give the imine product.[70]

Another route to *N*-tosyl imines is the preparation of a sulfinyl adduct **3.94** from the aldehyde, a sulfonamide and *p*-tolylsulfinic acid (Route **F**). This can then release the imine by

elimination on treatment with base often *in situ* during the addition reaction. This is particularly powerful for the synthesis of aliphatic imines.[219] Finally, oxidation of *N*-sulfinyl imines **3.95** with *m*-CPBA (Route **G**) is another route to *N*-tosyl imines.[220]

3.4.3 Methyl Addition to *Bis*-Sulfamyl Imine

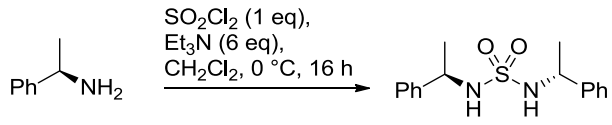


3.85a **3.96** 70%

Scheme 80

Addition of an excess of methylmagnesium bromide to imine **3.85a** gave **3.96** in a 1:1 ratio of the *rac*- and *meso*-diastereoisomers (Scheme 80). The diastereoisomers were distinguishable by ^{1}H NMR spectroscopy; however, the diastereoisomers could not be separated on TLC or by crystallisation. The *rac*- and *meso*-diastereoisomers were synthesised separately to confirm the ^{1}H NMR assignment.

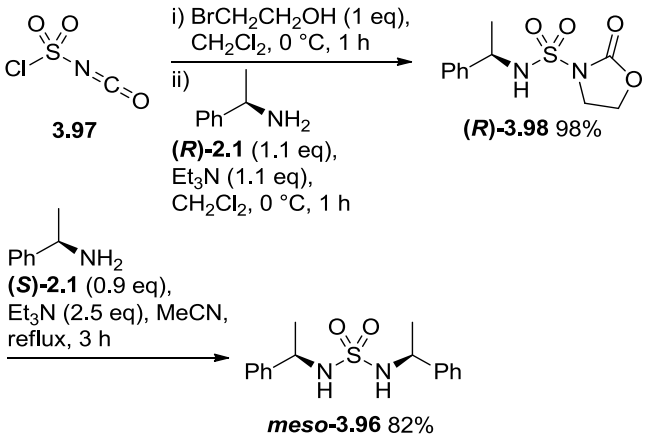
3.4.3.1 Synthesis of Diastereoisomers



(***R***)-**2.1** (2.1 eq) (***R,R***)-**3.96** 23%

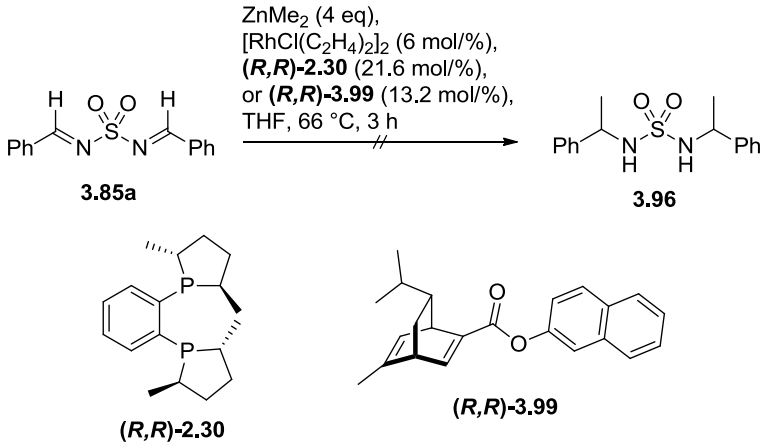
Scheme 81

The *rac*-diastereoisomer **(*R,R*)-3.96** was synthesised from the commercial (*R*)-1-phenylethylamine **(*R*)-2.1** and sulfuryl chloride (Scheme 81).[221] Synthesis of the *meso*-diastereoisomer required a route wherein two different amines could be introduced in a controlled fashion. Borghese *et al.*[222] described a route to non-symmetrical sulfamides using an *N*-sulfamoyloxazolidinone intermediate such as **(*R*)-3.98** (Scheme 82). This methodology was used to make ***meso*-3.96** in good yield. Other routes to unsymmetrical sulfamides will be discussed in Section 4.5.



Scheme 82

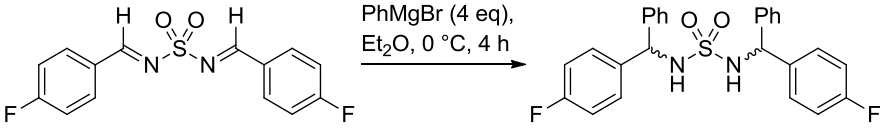
3.4.3.2 Asymmetric Methyl Addition



Scheme 83

Subjecting this imine **3.85a** to the optimised rhodium-catalysed dimethylzinc addition (see Section 2.4.5) gave no desired product using either (*R,R*)-MeDuPHOS **(*R,R*)-2.30** or Hayashi diene **(*R,R*)-3.99**[172] as the ligand (Scheme 83). With ligand **(*R,R,R*)-3.99** only reduction of the imine was observed. The reactions were also run using the higher concentrations typical of Hayashi's protocols[172] but again with no success. It was therefore, decided to focus on aryl additions to give diarylmethylamine products.

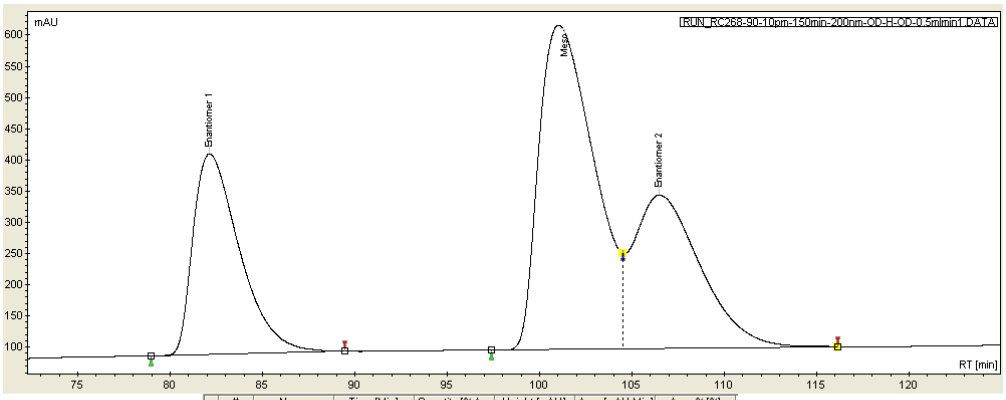
3.4.4 Aryl Addition to *Bis*-Sulfamyl Imines



3.85b (1 eq) **3.100b** 62%

Scheme 84

Phenylmagnesium bromide addition to the 4-fluoro imine **3.85b** also gave a 1:1 mixture of *rac*- and *meso*-diastereoisomers of addition product **3.100b** (Scheme 84). Unlike the methyl addition products, the two diastereoisomers were indistinguishable by ^{1}H NMR spectroscopy. In the ^{13}C NMR spectrum, some diastereotopic peaks were seen and a clear doublet was present in the ^{19}F NMR spectrum. Chiral HPLC showed three peaks in a ratio of 1:2:1, from the two enantiomers of the *rac*-diastereoisomer and the *meso*-diastereoisomer (Figure 1).

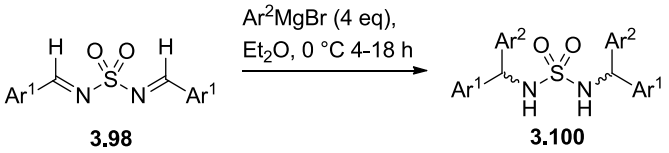


#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	Enantiomer 1	82.13	24.86	321.3	935.4	24.860
2	Meso	101.03	47.60	519.6	1791.1	47.602
3	Enantiomer 2	106.47	27.54	245.7	1036.2	27.538
Total			100.00	1086.5	3762.8	100.000

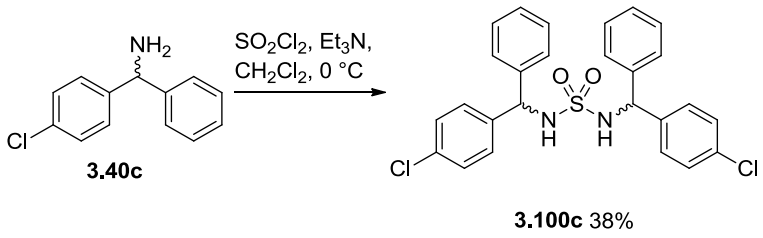
Figure 1

Mixtures of diastereoisomers of the addition product **3.100** were prepared by aryl Grignard reagent additions to the imines, these all occurred in good yield (Table 26). Addition product **3.100c** was made from (4-chlorophenyl)(phenyl)methanamine **3.40c** and sulfuryl chloride (Scheme 85). Chiral HPLC conditions were then developed for all the addition products.

Table 26



Entry	Ar^1	Ar^2	Sulfamide	**3.100** [%]
1	Ph	Ph	**3.100a**	78
2	4-FC_6H_4	Ph	**3.100b**	62
3	Ph	4-MeC_6H_4	**3.100d**	76
4	2-MeC_6H_4	Ph	**3.100e**	69
5	4-$MeOC_6H_4$	Ph	**3.100f**	65
6	Ph	4-$CO_2EtC_6H_4$	**3.100g**	43
7	3-MeC_6H_4	Ph	**3.100h**	67
8	4-BrC_6H_4	Ph	**3.100i**	86
9	4-FC_6H_4	4-MeC_6H_4	**3.100j**	74

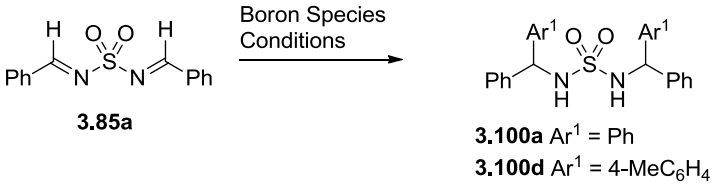


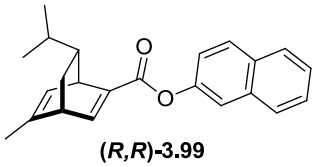
Scheme 85

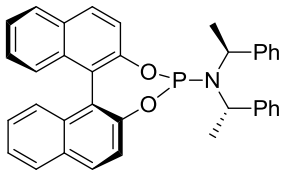
3.4.4.1 Addition of Aryl Boron Nucleophiles

A range of conditions for adding aryl boron nucleophiles were tested, with Hayashi's conditions for adding phenyl boroxine being by far the most successful (Entry 5, Table 27).

Table 27



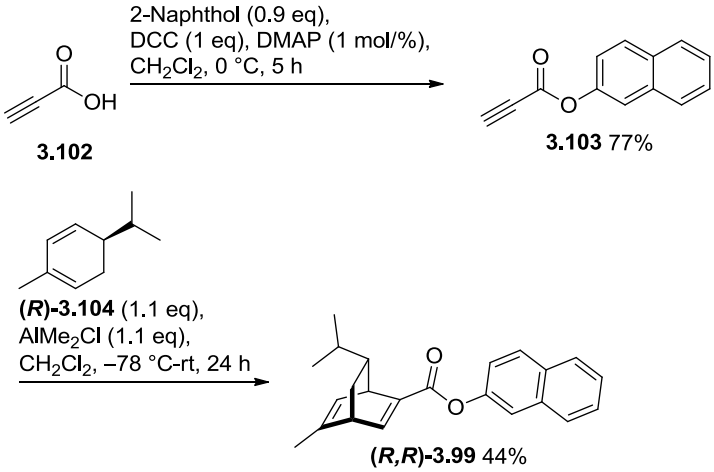

(*R,R*)-**3.99**


(*S,S,S*)-**2.42** (*S,S,S*)-Feringa

Entry	Boron species	Conditions	**3.100** [%][a]
1	4-MePhB(OH)$_2$ **3.25d** (2.6 eq)	[RhCl(C$_2$H$_4$)$_2$]$_2$ (3 mol/%), (*S,S,S*)-**2.42** (14 mol/%), acetone, 40 °C, 4 h[178]	0
2	4-MePhB(OH)$_2$ **3.25d** (4 eq)	[RhCl(C$_2$H$_4$)$_2$]$_2$ (3 mol/%), (*R,R,R*)-**3.99** (6.6 mol/%), Et$_3$N (4 eq), toluene, 55 °C, 5 h[175]	trace
3	4-MePhB(OH)$_2$ **3.25d** (4 eq)	[RhCl(C$_2$H$_4$)$_2$]$_2$ (3 mol/%), (*R,R,R*)-**3.99** (6.6 mol/%), CsF (4 eq), toluene, 55 °C, 5 h	0
4	[PhBF$_3$]K **3.101** (4 eq)	[RhCl(C$_2$H$_4$)$_2$]$_2$ (3 mol/%), (*R,R,R*)-**3.99** (6.6 mol/%), toluene, 55 °C	0
5	(PhBO)$_3$ **3.28a** (2.4 eq)	[RhCl(C$_2$H$_4$)$_2$]$_2$ (1.5 mol/%), (*R,R,R*)-**3.99** (3.3 mol/%), KOH$_{(aq)}$ (40 mol/%), dioxane, 60 °C, 3 h[172]	93/77[b]

[a] Conversion from crude ^{1}H NMR spectrum; [b] Isolated yield.

Phenyl boroxine **3.28a** (see Section 3.2.6) was made from phenyl boronic acid by azeotropic removal of water. Hayashi's diene ligand (*R,R,R*)-**3.99** was made from (*R*)-α-phelladrene (*R*)-**3.104** *via* a cycloaddition with naphthalen-2-yl propiolate **3.103** (Scheme 86).[172] This is a much more convenient synthesis than some of the other diene ligands, see Section 3.2.7.

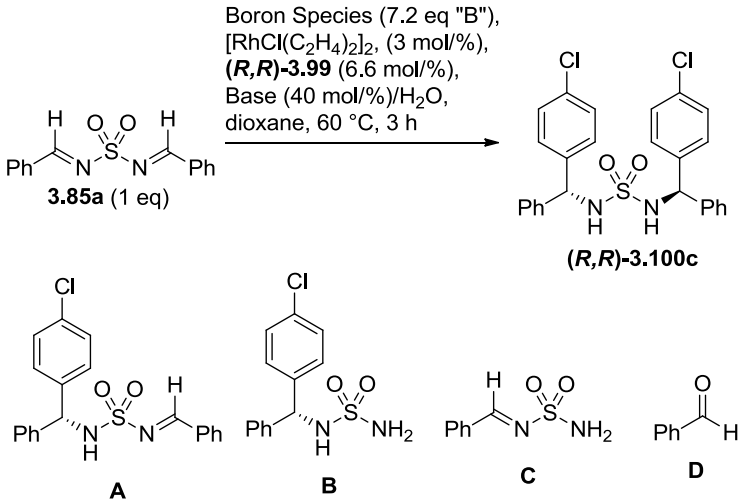


Scheme 86

3.4.4.2 Optimisation of Aryl Addition

This reaction was repeated with a substituted aryl boroxine so the enantioselectivity of the reaction could be studied. Addition of 4-chlorophenyl boroxine **3.28c** under the same conditions gave the mono-addition product **A** (see below) as the major product. A range of partial addition and hydrolysis products were seen in the crude ^{1}H NMR spectrum. A screen of conditions was carried out using potassium hydroxide and caesium fluoride as base, with varying amounts of water and boron species (Table 28). All reactions were run for 3 h in dioxane and the conversions were determined from the crude ^{1}H NMR spectra. However, at 60 °C at most 15% conversion to *bis*-addition **(*R*,*R*)-3.100c** was seen (Entry 2) but with 63% of mono-addition **A** this was an encouraging result.

Table 28[a]



Entry	Boron Species	Base	**(*R,R*)-3.100c**[b]	**A**[b]	**B**[b]	**C**[b]	**3.85a**[b]	**D**[b]
1	**3.25c**	$KOH_{(aq)}$	6	57	15	14	1	8
2	**3.28c**	$KOH_{(aq)}$	15	63	12	8	0	1
3	**3.28c**	$KOH_{(aq)}$[c]	0	0	0	36	0	64
4	**3.28c**	KOH[d]	0	11	0	24	48	17
5	**3.28c**	H_2O[e]	0	54	0	12	26	8
6	**3.28c**	CsF[d]	0	42	0	14	39	5
7	**3.28c**	$CsF_{(aq)}$	1	52	9	7	13	17

[a] Reactions were carried out using imine **3.85a** (0.25 mmol), $(4\text{-}ClC_6H_4BO)_3$ **3.28c** (0.6 mmol) or $4\text{-}ClC_6H_4B(OH)_2$ **3.25c** (1.8 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol/%), **(*R,R,R*)-3.99** (6.6 mol/%), base (40 mol/%) and (Entries 1, 2 and 7) H_2O (1.8 mmol) in dioxane (1.6 mL) at 60 °C for 3 h; [b] from crude ^1H NMR spectrum; [c] 3.1 M $KOH_{(aq)}$, 161 µL, 1 eq; [d] no water added; [e] 3.6 eq, 1.8 mmol H_2O.

Some of these conditions (Entries 1, 2, 5-7, Table 28) were then run at 80 °C (Table 29) in an aim to increase the rate of aryl addition. Interestingly the aryl boroxine **3.28c** performs much better than the aryl boronic acid **3.25c** (Entry 2 *vs.* 1). As under the reaction conditions the aryl boroxine and water are in equilibrium with the aryl boronic acid this difference seems strange. It may be that using the aryl boroxine and adding water allows the amount of water to be more closely controlled then using the boronic acid.[223] Another noteworthy point is that adding the

aqueous base by syringe pump improved the conversion (Entry 3 *vs.* 2). Caesium fluoride was found to be as good as potassium hydroxide as the base (Entry 3 *vs.* 6).

Table 29[a]

Entry	Boron Species	Base	***(R,R)*-3.100c**[b]	**A**[b]	**B**[b]	**3.85a**[b]	**C**[b]	**D**[b]	*dr*[c]	*ee* [%][c]
1	**3.25c**	$KOH_{(aq)}$	12	47	13	3	22	0	-	-
2	**3.28c**	$KOH_{(aq)}$	66	19	13	0	0	3	94:6	>99 (*R,R*)[d]
3	**3.28c**	$KOH_{(aq)}$[e]	81	14	4	0	0	2	93:7	>99 (*R,R*)[d]
4	**3.28c**	H_2O[f]	35	38	24	0	0	3	-	-
5	**3.28c**	CsF[g]	4	61	0	28	6	0	-	-
6	**3.28c**	$CsF_{(aq)}$	81	9	10	0	0	0	-	-

[a] Reactions were carried out using imine **3.85a** (0.25 mmol), $(4\text{-}ClC_6H_4BO)_3$ **3.28c** (0.6 mmol) or $4\text{-}ClC_6H_4B(OH)_2$ **3.25c** (1.8 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol/%), ***(R,R,R)*-3.99** (6.6 mol/%), base (40 mol/%) and (Entries 1-3, 6) H_2O (1.8 mmol) in dioxane (1.6 mL) at 80 °C for 3 h; [b] from crude ^1H NMR spectrum; [c] determined by HPLC using Chiralcel OD-H and Chiralcel OD columns in series, 90:10 hexanes:^{i}PrOH; [d] stereochemistry determined by deprotecting and comparing the optical rotation with literature values; [e] added *via* syringe pump; [f] 3.6 eq, 1.8 mmol water; [g] no water added.

The best of these conditions were run at 100 °C (Table 30). The optimum conditions were found to using aqueous KOH (40 mol/%) as the base (Entry 2). At 100 °C this gave a conversion of 91% of the *bis*-addition product ***(R,R)*-3.100c**; this reaction also gave the best diastereomeric ratio.

Table 30[a]

Entry	Boron Species	Base	***(R,R)*-3.100c**[b]	**A**[b]	**B**[b]	**3.85a**[b]	**C**[b]	**D**[b]	*dr*[c]	*ee* [%][c]
1	**3.25c**	$KOH_{(aq)}$	16	32	32	2	15	3	-	-
2	**3.28c**	$KOH_{(aq)}$	91	0	9	0	0	0	95:5	>99 (*R,R*)[d]
3	**3.28c**	$CsF_{(aq)}$	82	3	15	0	0	0	92:8	>99 (*R,R*)[d]

[a] Reactions were carried out using imine **3.85a** (0.25 mmol), $(4\text{-}ClC_6H_4BO)_3$ **3.28c** (0.6 mmol) or $4\text{-}ClC_6H_4B(OH)_2$ **3.25c** (1.8 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol/%), ***(R,R,R)*-3.99** (6.6 mol/%), base (40 mol/%) and (Entries 1, 2, 5-7, 10 and 11) H_2O (1.8 mmol) in dioxane (1.6 mL) at 100 °C for 3 h; [b] from crude ^1H NMR spectrum; [c] determined by HPLC using Chiralcel OD-H and Chiralcel OD columns in series, 90:10 hexanes:^{i}PrOH; [d] stereochemistry determined by deprotecting and comparing the optical rotation with literature values.

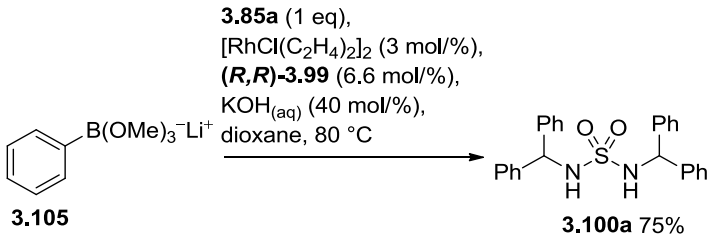
Next the amount of aryl boroxine **3.28c** required was investigated; so far each reaction had been run with 1.2 equivalents of aryl boroxine (3.6 equivalents "Ar-B") with respect to the imine functional group and it was hoped that this could be reduced. However, as Table 31 shows as the equivalents of aryl boroxine **3.28c** are reduced the amount of hydrolysis products increases, even when the amount of base is reduced in keeping with the equivalents of boroxine.

Table 31[a]

Entry	**3.28c** [Eq]	**(*R,R*)-3.100c**[b]	**A**[b]	**B**[b]	**3.85a**[b]	**C**[b]	**D**[b]
1	1.2	81	3	16	0	0	0
2	0.8	78	3	19	0	0	0
3	0.8[c]	78	8	12	0	1	0
4	0.4	37	8	15	1	18	21
5	0.4[c]	24	62	12	0	3	0
6	0.3	0	0	0	4	53	43
7	0.3[c]	16	70	7	0	5	2

[a] Reactions were carried out using imine **3.85a** (0.25 mmol), $(4\text{-}ClC_6H_4BO)_3$ **3.28c**, $[RhCl(C_2H_4)_2]_2$ (3 mol/%), **(*R,R,R*)-3.99** (6.6 mol/%), 3.1 M $KOH_{(aq)}$ (40 mol/%) in dioxane (1.6 mL) at 100 °C for 3 h; [b] from crude ^1H NMR spectrum; [c] $KOH_{(aq)}$ scaled down *pro rata* from 0.1 mmol to 0.066, 0.083 or 0.028 mmol respectively.

So far, only aryl boroxine and aryl boronic acid nucleophiles had been added. It was decided to look at what other boron species could be used with the aim of reducing the number of equivalents used.



Scheme 87

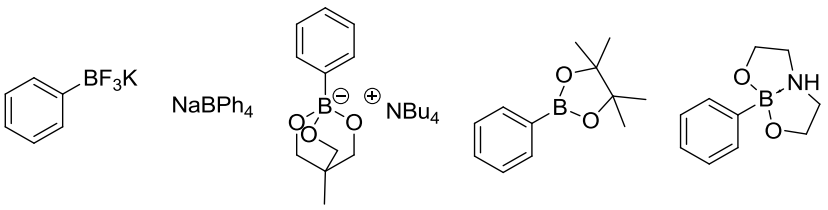
Hayashi had successfully used the lithium aryl boronate **3.105** in his 1,4-addition to α-β-unsaturated esters.[224] The boronate was prepared by lithiation of bromobenzene and

trapping with trimethoxyborane, addition of this to imine **3.85** (Scheme 87) proceeded in equivalent yield to the addition of phenyl boroxine (Entry 5, Table 27).

This result and the need for water to be present suggests that quaternarisation of the boron is required for the reaction to proceed. The nucleophilicity of the organic group can be increased by coordination of a negatively charged base to the boron atom.[28] Therefore, various boronate species were trailed in the reaction.

Sodium trihydroxyborates can be isolated are free flowing powders and then subsequently used in cross-coupling reactions.[225] Sodium trihydroxyphenylborate was preformed[226] and added to the reaction; this gave an encouraging yield of the mono-addition product (Entry 1, Table 32). With phenyl potassium trifluoroborate **3.101,** no addition product was observed (Entry 3). Sodium tetraphenyl borate gave a moderate yield of the mono-addition product **A** (Entry 4); however, it does not help reduce the number of "Ar-B" equivalents in use. The triol boronate species **3.106** was investigated, but lead to only hydrolysis of the imine rather than addition (Entry 5). The pinacol boronic ester **3.107** and self-activating boronic ester **3.108**[227] also gave no addition products with or without base (Entries 6-9).

Table 32[a]



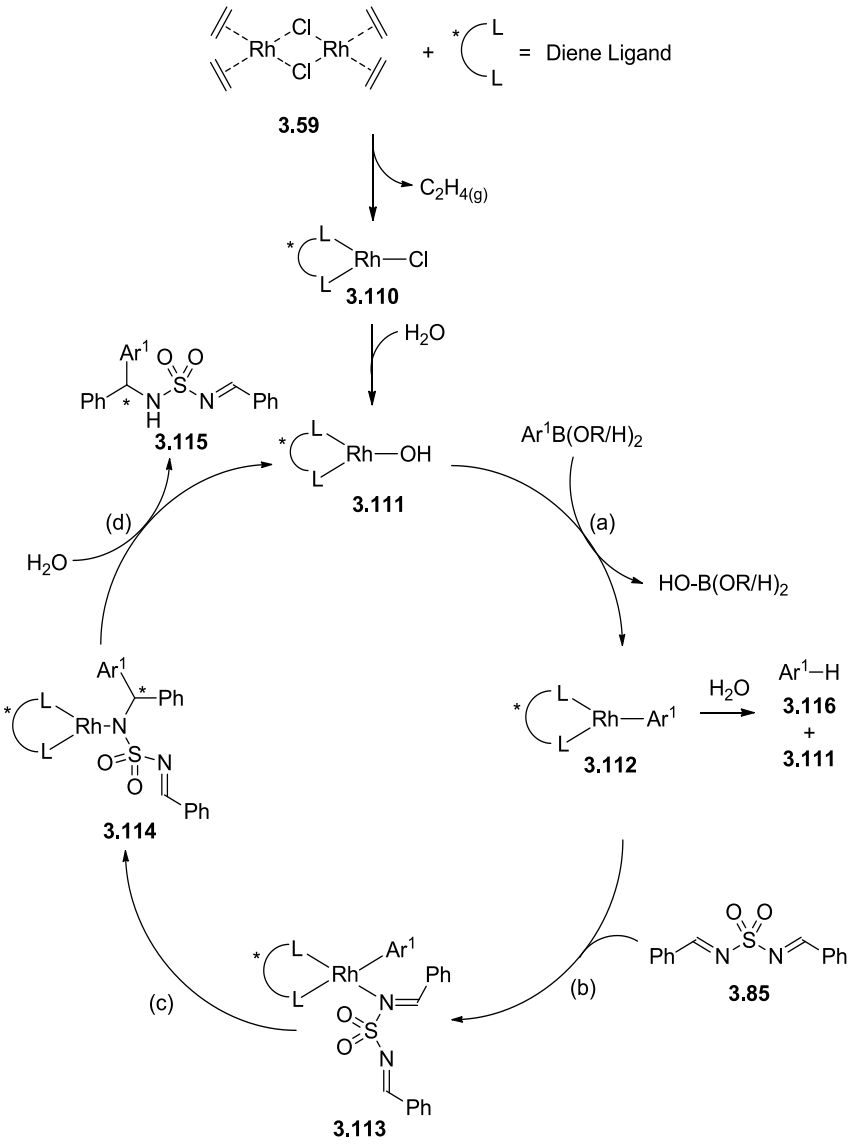
3.101 **3.29** **3.106** **3.107** **3.108**

Entry	Boron Species	Additive	**3.100a**[b]	**A**[b]	**B**[b]	**3.85**	**C**[b]	**D**[b]
1	$[PhB(OH)_3Na]$ **3.109a**		19	70	5	0	6	1
2	$PhB(OH)_2$	H_3BO_3	21	44	19	1	16	0
3	**3.101** (60 °C)		0	0	0	69	28	2
4	**3.29**		26	55	0	0	1	18
5	**3.106**		0	0	0	5	45	50
6	**3.107**		0	0	0	100	0	0

7	**3.107**	$KOH_{(aq)}$	0	0	0	1	9	90
8	**3.108**		0	0	0	58	42	0
9	**3.108**	$KOH_{(aq)}$	0	0	0	4	26	70

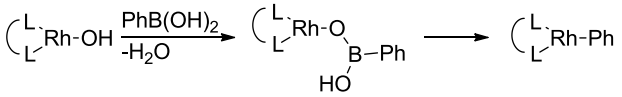
[a] Reactions were carried out using imine **3.85a** (0.25 mmol), Boron Species (0.6 mmol, except entry 1: 1.8 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol/%), ***(R,R,R)*-3.99** (6.6 mol/%), (Entry 7 and 9) 3.1 M $KOH_{(aq)}$ (40 mol/%) in dioxane (1.6 mL) at 100 °C (except entry 3) for 3 h; [b] from crude ^1H NMR spectrum, addition and hydrolysis products shown in Table 28 however, unsubstituted in this case.

3.4.4.3 Mechanism and Stereochemistry



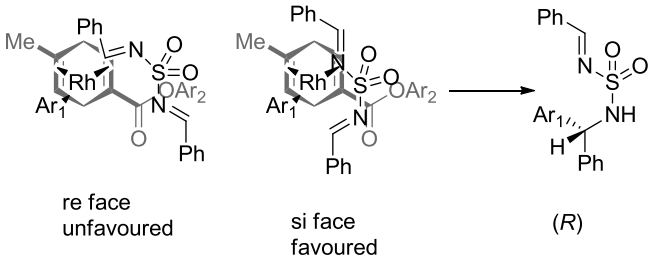
Scheme 88

The accepted mechanism for the rhodium catalysed boronic acid/boroxine addition is shown in Scheme 88.[31] The ethylene ligands of the precursor **3.59** are displaced by the chiral diene ligand; typically these two components are stirred together before the addition of the substrates to ensure complete ligand exchange to species **3.110**. Transmetallation of **3.110** with the aryl boronic acid is very slow, it is thought that rhodium hydroxide species **3.111** is formed and then fast transmetallation occurs to give aryl rhodium complex **3.112**.[31] The imine **3.85** then coordinates (b) and then (c) the imine inserts into the rhodium-carbon bond, in an enantioselective manner when chiral ligands are present.[228] The rhodium amide **3.114** is then hydrolysed (d) to regenerate the active hydroxo-rhodium complex **3.111**. The rhodium hydroxide and aryl rhodium complexes with (*S*)-BINAP **(*S*)-1.34** as the ligand have been observed by ^{31}P NMR spectroscopy in the rhodium catalysed 1,4-addition of boronic acids to enones.[36] A possible side reaction is the hydrolytic protodeboronation of the aryl boron reagent, i.e. hydrolysis of the aryl-rhodium complex **3.112**, to give the catalytic species **3.111** and aromatic **3.116** (Scheme 88), before it reacts with the imine. Increasing the equivalents of boron nucleophile is a common way of getting around this. It is thought that the transmetallation occurs though β-elimination from the intermediate shown in Scheme 89.[229]



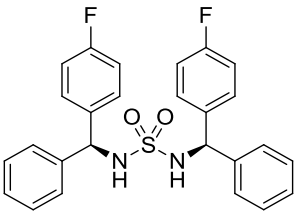
Scheme 89

The absolute stereochemistry of the product is consistent with Hayashi's own results using this ligand.[172] The aryl-rhodium bond will form *trans* to the double bond bearing the electron-withdrawing ester group. The imine will coordinate in the remaining free site; the *si*-face of the imine is preferred to avoid a steric clash between the ester substituent and the sulfamide group (Scheme 90).



Scheme 90

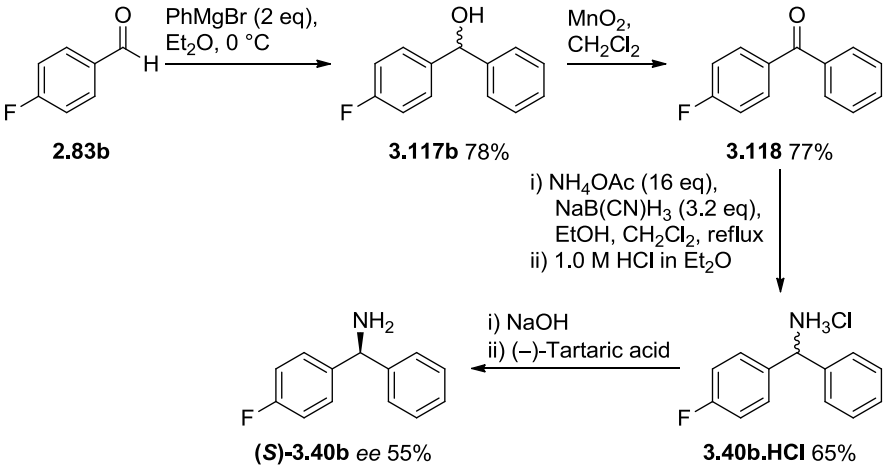
3.4.4.4 Synthesis of *Meso*-Diastereoisomer



***meso*-3.100b**

Scheme 91

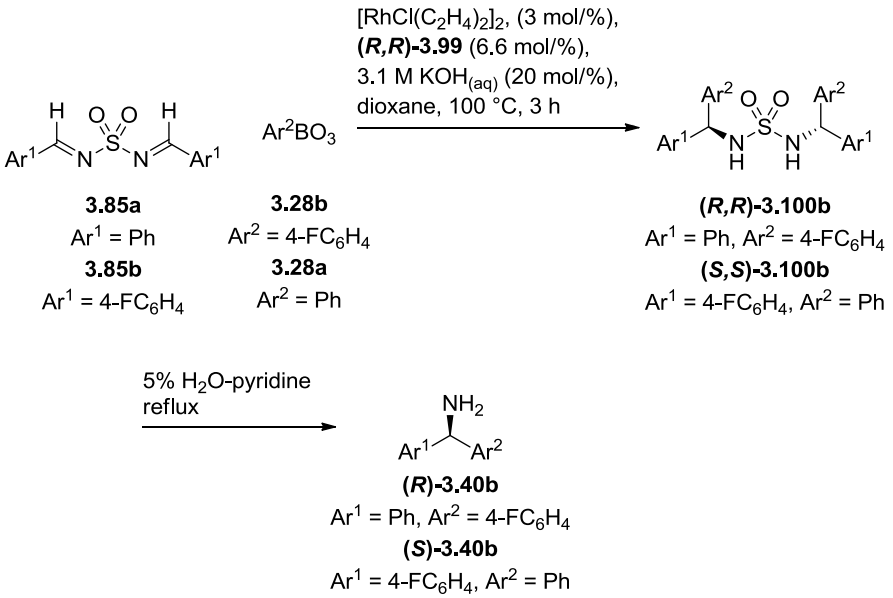
It was decided to synthesise the *meso*-diastereoisomer of the 4-fluorophenyl addition product ***meso*-3.100b** (Scheme 91) so the peaks seen by HPLC and the diastereotopic peaks in the ^{19}F NMR spectrum could be assigned. To make this compound both enantiomers of (4-fluorophenyl)(phenyl)methanamine **3.40b** were required. Firstly resolution of racemic (4-fluorophenyl)(phenyl)methanamine with tartaric acid was attempted; this was not a known resolution but the method had been reported with (4-chlorophenyl)(phenyl)methanamine.[230] The racemic amine was made from 4-fluorobenzaldehyde **2.83b** using a Grignard reagent addition, oxidation and reductive amination (Scheme 92).



Scheme 92

Unfortunately, attempted resolution using (–)-tartaric acid gave an enantiomeric excess of only 55% (determined by chiral HPLC on the acetamide). So a new approach was employed using the asymmetric rhodium-catalysed aryl addition and subsequent deprotection to make both enantiomers from the appropriately substituted starting materials (Table 33).

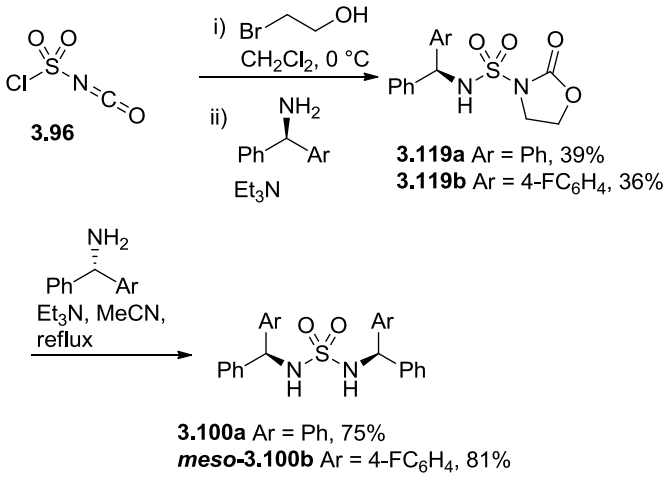
Table 33



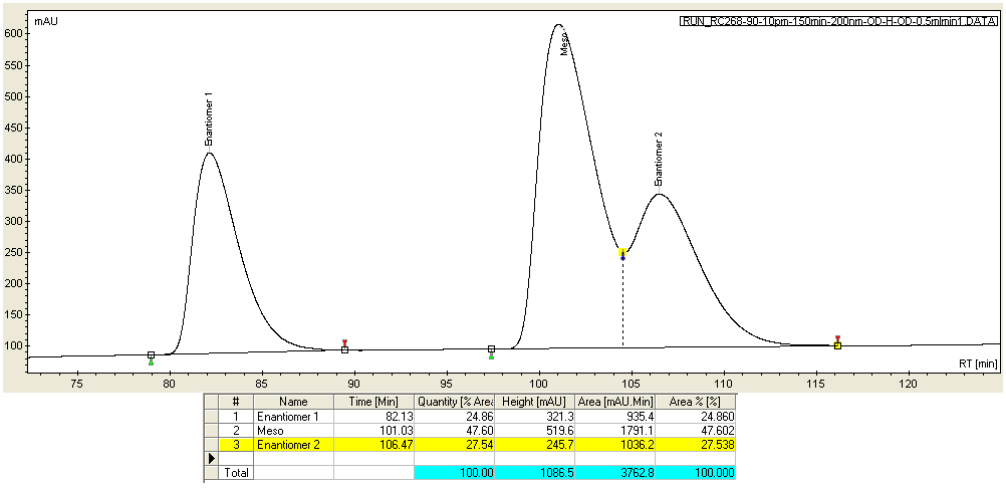
Entry	Ar^1	Ar^2	**3.100b** [%]	*dr*[a]	*ee* [%][a]	**3.40b** [%]	*ee* [%][b]
1	Ph	4-FC_6H_4	46	96:4	>99 (*R*,*R*)	85	90 (*R*)
2	4-FC_6H_4	Ph	75	94:6	86 (*S*,*S*)	86	86 (*S*)

[a] Determined by HPLC using Chiralcel OD-H and Chiralcel OD columns in series, 90:10 hexanes:^{i}PrOH; [b] determined on the acetamide by HPLC using Chiralcel OD, 90:10 hexanes:^{i}PrOH.

As both enantiomers have been synthesised the *meso* peak on the HPLC can be identified by elimination. Nevertheless, for completeness the *meso*-diastereoisomer was made using the route discussed in Section 3.6.2. Firstly, the route was trialled using aminodiphenylmethane **3.40a** and then the enantiomers prepared above were used to make ***meso*-3.100b** (Scheme 93). The resulting HPLC traces of the *rac*: *meso* mixtures, both *rac*-enantiomers and the *meso*-diastereoisomer are shown below (Figures 2-5).

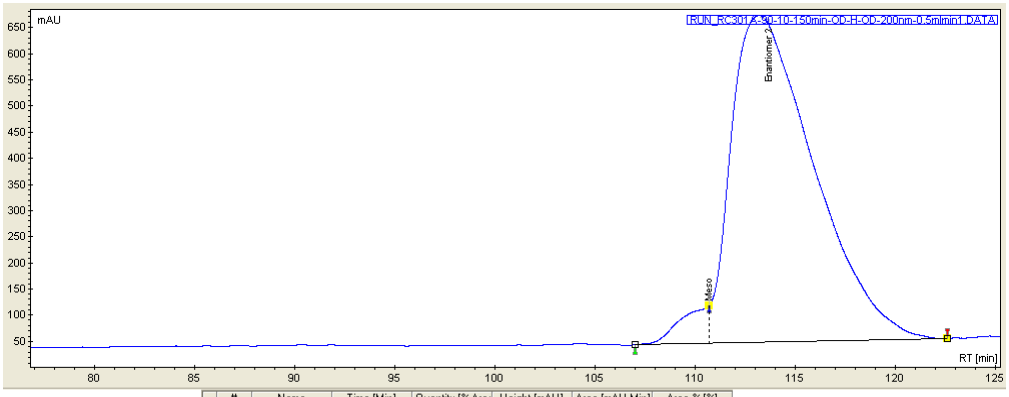


Scheme 93



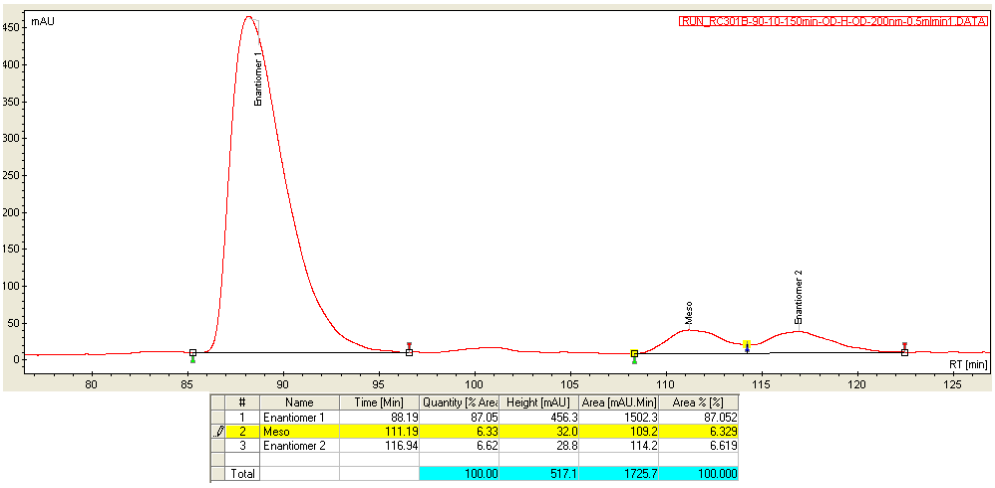
#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	Enantiomer 1	82.13	24.86	321.3	935.4	24.860
2	Meso	101.03	47.60	519.6	1791.1	47.602
3	Enantiomer 2	106.47	27.54	245.7	1036.2	27.538
Total			100.00	1086.5	3762.8	100.000

Figure 2: HPLC trace of 1:1 ***rac*: *meso*-3.100b**



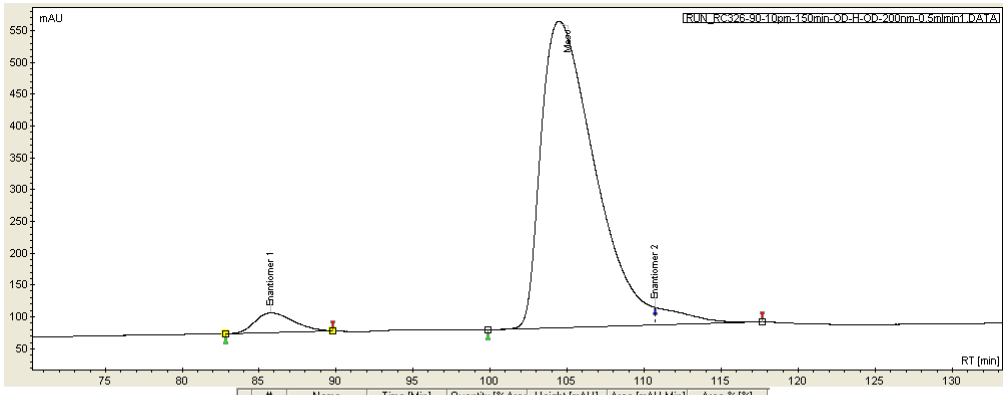
#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	Meso	110.68	3.82	71.8	118.4	3.818
2	Enantiomer 2	113.19	96.18	625.3	2981.5	96.182
Total			100.00	697.2	3099.9	100.000

Figure 3: HPLC trace of **(*R*,*R*)-3.100b**



#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	Enantiomer 1	88.19	87.05	456.3	1502.3	87.052
2	Meso	111.19	6.33	32.0	109.2	6.329
3	Enantiomer 2	116.94	6.62	28.8	114.2	6.619
Total			100.00	517.1	1725.7	100.000

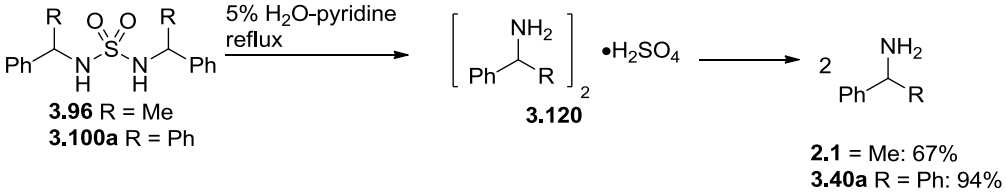
Figure 4: HPLC trace of **(*S*,*S*)-3.100b**



#	Name	Time [Min]	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	Enantiomer 1	85.77	4.26	30.8	88.6	4.257
2	Meso	104.47	92.58	481.9	1928.2	92.584
3	Enantiomer 2	110.70	3.16	27.5	65.8	3.159
Total			100.00	540.2	2082.6	100.000

Figure 5: HPLC trace of ***meso*-3.100b**

3.4.5 Deprotection of Addition Products

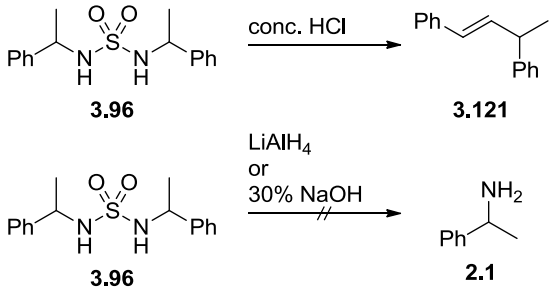


Scheme 94

The addition products were then deprotected to the amines under the mild conditions stated in the paper of Davis *via* the hydrogen sulfate salt **3.120**.[207] The diphenyl compound gave a higher yield than the methyl addition product (Scheme 94).

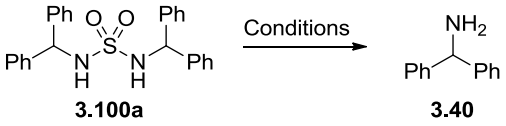
To understand the mechanism of the hydrolysis other conditions were investigated. Davis[207] also reported that attempted hydrolysis of the methyl addition product **3.96** with

conc. HCl gave 1,3-diphenyl-1-butene **3.121** (Scheme 95). This sulfamide was also found to be unreactive to $LiAlH_4$ and 30% NaOH.[207]



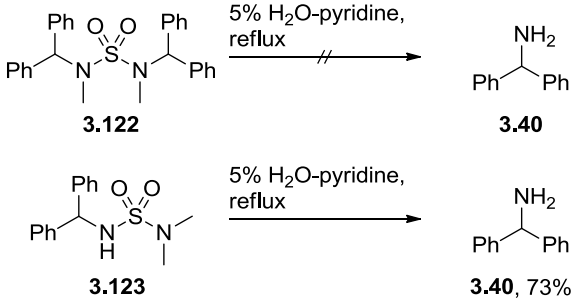
Scheme 95

Table 34

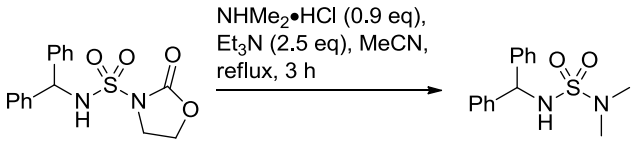


Entry	Conditions	Result
1	H_2O, 100 °C, 18 h	Recovered starting material
2	2 M $HCl_{(aq)}$, 100 °C, 18 h	Recovered starting material
3	5% H_2O-MeCN, 82 °C, 18 h	Recovered starting material
4	DMAP (5 mol/%), 5% H_2O-MeCN, 82 °C, 18 h	Recovered starting material

Sulfamide **3.100** gave no hydrolysis product after reflux in water or dilute aqueous acid (Entries 1 and 2, Table 34). However, this may have been due to its insolubility in these systems. Therefore, hydrolysis was attempted in aqueous acetonitrile (Entry 3) and in the presence of DMAP (Entry 4) but still, no hydrolysis product was observed.



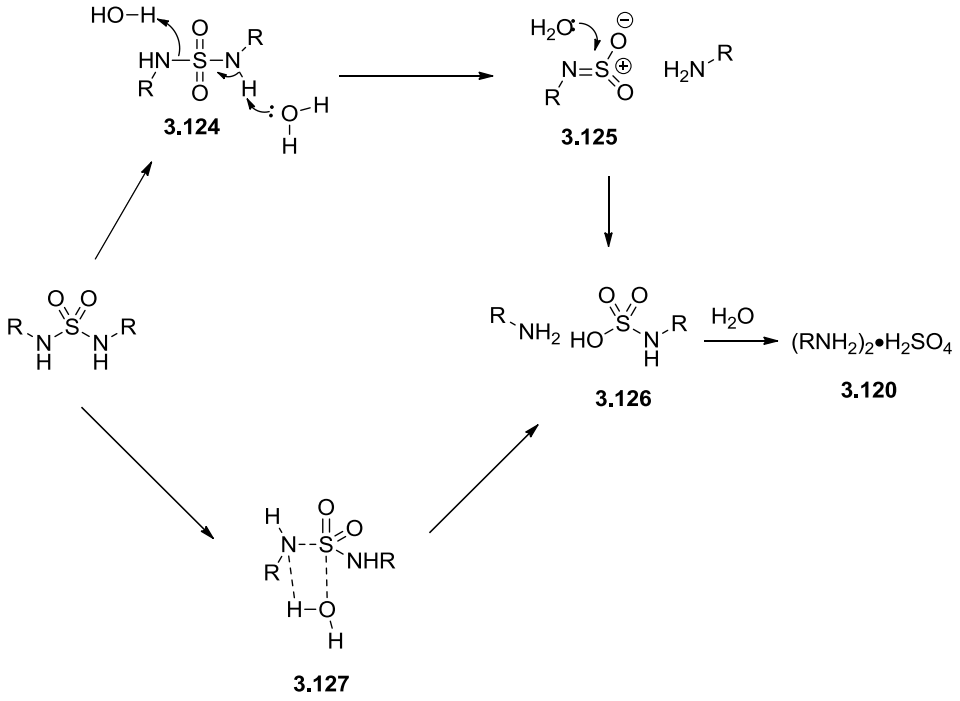
Scheme 96



3.119a **3.123** 59%

Scheme 97

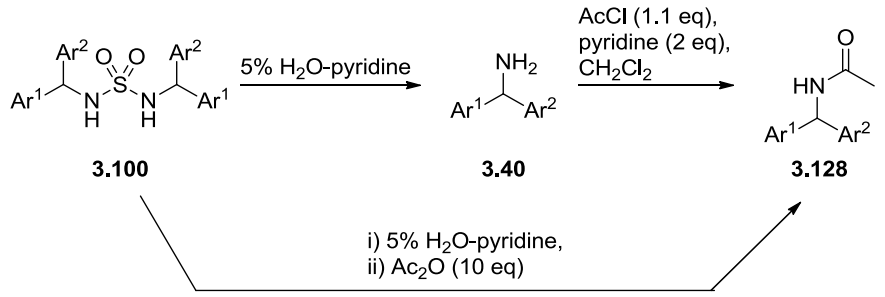
It was found that when both nitrogen atoms were substituted with methyl groups **3.122** that deprotection no longer occurred under the aqueous pyridine conditions and only starting material was recovered (Scheme 96). Similarly Davis found that when **3.96** was doubly *N*-benzylated hydrolysis no longer occurred with aqueous pyridine, however, Na-naphthalene conditions were successful.[207] So the presence of the free NH was crucial to the hydrolysis mechanism. Interestingly, in the case of unsymmetrical sulfamide **3.123** (synthesised as shown in Scheme 97) with only one free NH present deprotection still occurred in 73% yield.



3.124 **3.125** **3.126** **3.120** **3.127**

Scheme 98

Davis postulates a route involving pyridine induced hydrolysis to intermediate **3.125**[231] which can be attacked by water to give sulfamic acid **3.126** (Scheme 98). Sulfamic acids **3.126** are known to hydrolyse to hydrogen sulfate salts **3.120**.[232] *N*-Sulfonylamine **3.125** has been implicated in the mechanism of the reaction of sulfamoyl chlorides with anilines.[233-235] Spillane has hypothesised a hydrolysis *via* transition state **3.127**.[232]



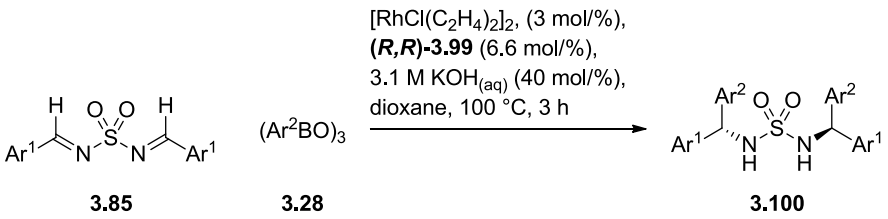
Scheme 99

The free amine must be derivatised as the acetamide before the enantiomeric excess can be measured by chiral HPLC. Pyridine acts as a catalyst for acylations so it is possible to make the acetamide in one pot without isolating the free amine **3.40** (Scheme 99).

3.4.6 Scope

With optimised aryl addition conditions and a mild deprotection in hand, the scope of the reaction was investigated.

Table 35[a]



Entry	Ar^1	Ar^2	Conversion [%][b]	Yield [%]	*dr*[c]	*ee* [%][c]
1	Ph	4-FC_6H_4	85	69 **(*R*,*R*)-3.100b**	97:3	>99 (*R*,*R*)
2	Ph	4-ClC_6H_4	77	61 **(*R*,*R*)-3.100c**	94:6	>99 (*R*,*R*)[d]
3	Ph	4-MeC_6H_4	81	58 **(*R*,*R*)-3.100d**	93:7	>99 (*R*,*R*)
4	Ph	2-MeC_6H_4	77	71 **(*R*,*R*)-3.100e**	>99:1	90 (*R*,*R*)
5	Ph	4-$MeOC_6H_4$	92	72 **(*R*,*R*)-3.100f**	92:8	>99 (*R*,*R*)
6	Ph	4-$CO_2EtC_6H_4$	51	37 **(*R*,*R*)-3.100g**	97:3[e]	94 (*R*,*R*)[e]
7	4-FC_6H_4	Ph	100	73 **(*S*,*S*)-3.100b**	92:8	>99 (*S*,*S*)
8	4-MeC_6H_4	Ph	83	73 **(*S*,*S*)-3.100d**	92:8	>99 (*S*,*S*)

9	2-MeC_6H_4	Ph	79	69 **(*S*,*S*)-3.100e**	96:4	98 (*S*,*S*)
10	4-$MeOC_6H_4$	Ph	90	69 **(*S*,*S*)-3.100f**	95:5	>99 (*S*,*S*)
11	3-MeC_6H_4	Ph	89	75 **(*S*,*S*)-3.100h**	92:8	>99 (*S*,*S*)
12	4-BrC_6H_4	Ph	75	62 **(*S*,*S*)-3.100i**	91:9	>99 (*S*,*S*)[d]
13	4-FC_6H_4	4-MeC_6H_4	100	76 **(*S*,*S*)-3.100j**	91:9	98 (*S*,*S*)

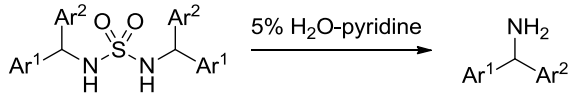
[a] Reactions were carried out using imine **3.85** (0.25 mmol), boroxine **3.28** (0.6 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol/%), **(*R*,*R*,*R*)-3.99** (6.6 mol/%), 3.1 M $KOH_{(aq)}$ (40 mol/%) in dioxane (1.6 mL) at 100 °C for 3 h; [b] From crude ^1H NMR spectrum; [c] determined by chiral HPLC (see Chapter 6: Experimental for conditions); [d] stereochemistry determined by deprotecting and comparing the optical rotation with literature values, other cases were assigned by analogy; [e] calculated from *ee* of derived acetate **3.128g**, a chiral HPLC method has yet to be found for **3.100g**.

Firstly, the unsubstituted imine **3.85a** was reacted with a range of aryl boroxines both electron-withdrawing groups (Entries 1 and 2, Table 35) and electron-donating groups (Entry 5) were tolerated. The yield for the boroxine bearing a *para*-ester group (Entry 6) was disappointing; it is possible that some hydrolysis occurred under the reaction conditions. The enantiomeric excess is excellent in most cases with the presumably the *ortho* substituent lowering the result to 90% in Entry 4 (although this case has the best diastereomeric ratio).

The substitution on the imine was investigated; again, electron-withdrawing groups (Entry 7) and electron-donating groups (Entry 10) are well tolerated. *Ortho*-substitution on the imine (Entry 9) has a smaller impact on the enantiomeric excess than on the boroxine.

It was hoped that recrystallisation would allow the *rac*:*meso* ratio to be improved upon. However, when the 4-fluoro addition product **(*S*,*S*)-3.100b** was recrystallised (both from hot ethanol and by liquid-liquid diffusion of CH_2Cl_2/hexanes) the diastereomeric ratio of the crystalline solid remained the same or become worse. The filtrate became enriched with the *rac*-diastereoisomer but this was less the 10% of the material.

Table 36



3.100 **3.40**

Entry	Ar^1	Ar^2	**3.40** [%]	Amine	*ee* [%][a]
1	Ph	4-FC_6H_4	80	**(*R*)-3.40b**	94 (*R*)
2	Ph	4-ClC_6H_4	93	**(*R*)-3.40c**	87 (*R*)[b]
3	Ph	4-MeC_6H_4	72	**(*R*)-3.40d**	92 (*R*)
4	Ph	2-MeC_6H_4	53	**(*R*)-3.40e**	97 (*R*)
5	Ph	4-$MeOC_6H_4$	95	**(*R*)-3.40f**	86 (*R*)
6	Ph	4-$CO_2EtC_6H_4$	31	**(*R*)-3.40g**	91 (*R*)
7	4-FC_6H_4	Ph	79	**(*S*)-3.40b**	82/91[c] (*S*)
8	4-MeC_6H_4	Ph	60	**(*S*)-3.40d**	92 (*S*)
9	2-MeC_6H_4	Ph	32	**(*S*)-3.40e**	96 (*S*)
10	4-$MeOC_6H_4$	Ph	85	**(*S*)-3.40f**	94 (*S*)
11	3-MeC_6H_4	Ph	73	**(*S*)-3.40h**	86 (*S*)
12	4-BrC_6H_4	Ph	61	**(*S*)-3.40i**	95 (*S*)[b]
13	4-FC_6H_4	4-MeC_6H_4	99	**(*S*)-3.40j**	92 (*S*)

[a] Measured on acetamide by chiral HPLC (see Experimental for conditions); [b] stereochemistry determined by comparison of the optical rotation with literature values, other cases were assigned by analogy; [c] after recrystallisation of HCl salt from water.

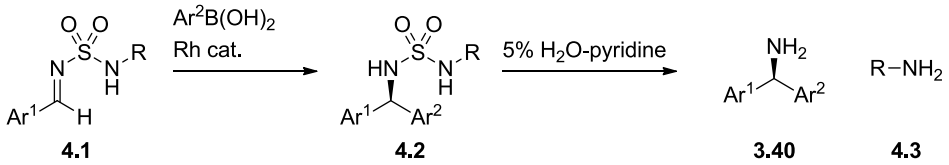
The chiral diarylmethylamines **3.40** were isolated in good enantiomeric excess, reflecting the diastereomeric ratio of the aryl addition. The yields were good in most cases with *ortho*-substitution again appearing to be detrimental (Entries 4 and 9, Table 36) and an isolation issue lowered the yield of the ester substituted amine (Entry 6). The enantiomeric excess of a free amine has been improved, by recrystallisation of the HCl salt from water, from 82% to 91% (Entry 7). It has been confirmed that no epimerisation occurs during the

deprotection by subjecting a free amine of known enantiomeric excess to the hydrolysis conditions.

Chapter 4

4.1 Aims and Objectives

The diastereoselectivity and subsequent inseparable diastereoisomers of the current rhodium catalysed aryl addition reaction, to *bis*-sulfamyl imines as described in Chapter 3, are its main limitations, as after deprotection the enantiomeric excess is lowered. The mildness of the deprotection makes this chemistry very attractive, so it was proposed that a mono-imine of the type **4.1** (Scheme 100) could be a useful substrate, where "R" is a low molecular weight alkyl group. After asymmetric addition of the aryl boronic acid the resulting unsymmetrical sulfamide **4.2** could be deprotected using the same mild conditions to give the enantioenriched amine **3.40** and a low molecular weight amine **4.3** that can easily be separated.

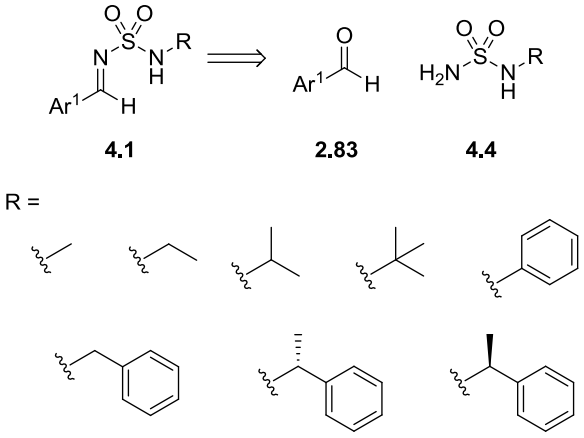


Scheme 100

It is thought that the presence of the NH in the protecting group is key to the ease of deprotection. When Davis alkylated this position the amine could no longer be deprotected.[207] From our own experience the *bis*-methylated sulfamide **3.122** could not be deprotected under these conditions (see Section 3.8). Feringa *et al.*[178] have used an *N,N*'-dimethylsulfamoyl activating group for the imine substrate undergoing aryl boronic acid addition. However, the deprotection of resulting amine **3.48**, although milder than tosyl deprotection did require prolonged heating in a microwave (see Section 3.2.6.1).

This type of imine is unprecedented in the existing literature, however, it was envisaged that these imines could be made from the condensation of an aryl aldehyde **2.83** with the appropriate mono-substituted sulfamide **4.4** (Scheme 101). We decided on a small set of R groups ranging from methyl to phenylethyl (Scheme 101), to investigate whether the steric bulk of the protecting group would influence the yield of the aryl addition or enantioselectivity and with the two enantiomers of phenylethyl whether there was a favoured enantiomer. The

sulfamides **4.4** would need to be synthesised on a large scale from readily available starting materials.

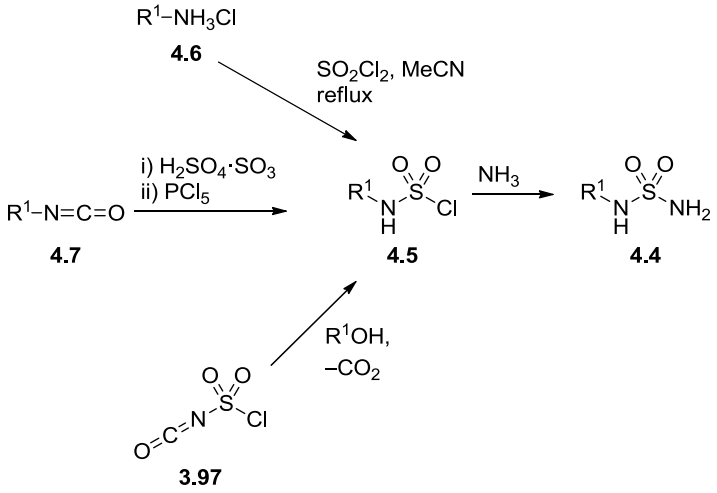


4.1 **2.83** **4.4**

Scheme 101

4.1.1 Sulfamide Synthesis

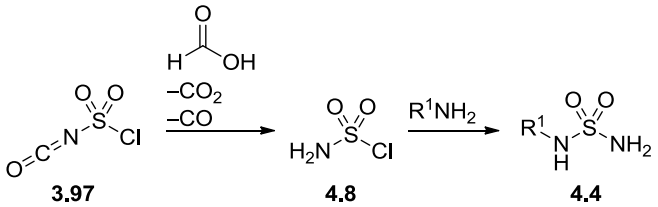
Primary sulfamides **4.4** can be prepared from the appropriate *N*-sulfamoyl chloride **4.5** and ammonia.[236,237] Few *N*-sulfamoyl chlorides **4.5** are commercially available. They can be made by a number of routes (Scheme 102), firstly by refluxing the hydrogen chloride salt of an amine **4.6** with excess sulfuryl chloride. However, this approach can be low yielding and is limited in amine scope.[238,239]



Scheme 102

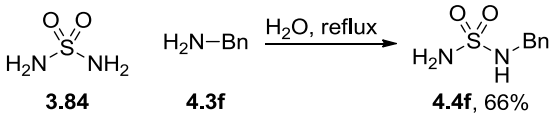
Secondly, *N*-sulfamoyl chlorides **4.5** can be prepared from an alkyl isocyanate **4.7** using the hazardous and corrosive materials of fuming sulfuric acid and phosphorus pentachloride.[240] Finally, addition of an alcohol to chlorosulfonyl isocyanate **3.97** (CSI) followed by elimination of carbon dioxide also gives the *N*-sulfamoyl chloride **4.5**.[241,242] Alternatively the

unsubstituted sulfamoyl chloride **4.8** can be synthesised from CSI **3.97** and formic acid and reacted immediately with an amine to give the primary sulfamide **4.4** (Scheme 103).[242]



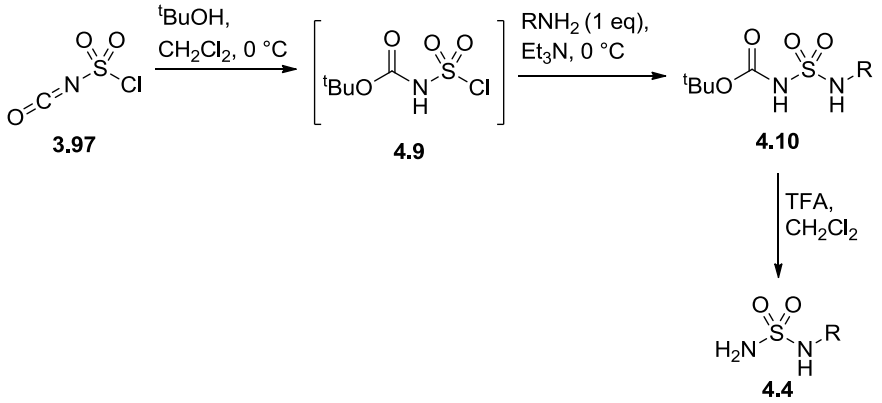
Scheme 103

Another method for non-volatile amines is the transamination of sulfamide. This method was used to prepare *N*-benzylsulfamide **4.4f** by displacement of sulfamide **3.84** with benzylamine **4.3f** (Scheme 104).[243] However, it was desirable to use a smaller alkyl group to keep the molecular weight of the activating group low. Therefore, as amines of a higher volatility than benzylamine needed to be used, another method for the synthesis of *N*-alkylsulfamides from chlorosulfonyl isocyanate was employed.



Scheme 104

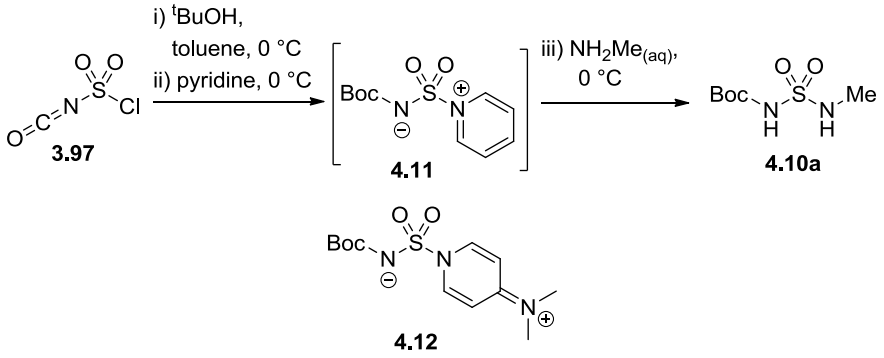
Chlorosulfonyl isocyanate **3.97** is prepared from cyanogen chloride and sulfur trioxide.[244] It is a powerful bielectrophile, but it is possible to react the isocyanate and the chlorosulfonic acid sequentially. Reacting chlorosulfonyl isocyanate sequentially with *tert*-butanol and a primary amine gives *N*-Boc-protected sulfamide **4.10** (Scheme 105).[245,246] Standard Boc-deprotection then gives the desired primary sulfamide **4.4**.



Scheme 105

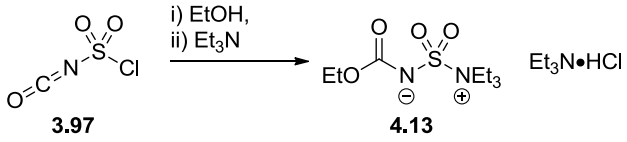
Masui *et al.*[247] adapted this approach for use with aqueous solutions of primary amines. As methylamine and ethylamine are typically available as their aqueous solutions, this is very

useful. CSI **3.97** is sequentially reacted with *tert*-butanol and pyridine to give a Burgess-type intermediate **4.11** (Scheme 106). This is reacted *in situ* with aqueous methylamine to give the *N*-Boc-protected sulfamide **4.10a**, which can be deprotected as before. 4-Dimethylaminopyridine has also been used to make a Burgess-type intermediate **4.12** which was stable enough to be isolated.[248]



Scheme 106

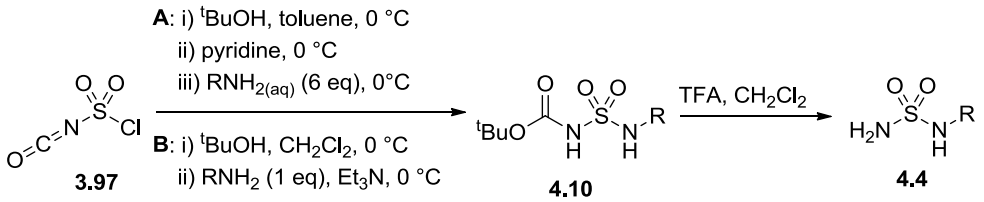
This type of intermediate was first reported in 1968 by the group of Burgess (Scheme 107).[249] Burgess salts have been employed as a dehydration agents to convert secondary or tertiary alcohols to alkenes[250] or amides to nitriles.[251] Another use of Burgess salts is the preparation of carbamates from alcohols[252] or in the synthesis of unsymmetrical sulfamides from aminoalcohols or amines[253,254] and the synthesis of sulfamidates from diols.[254]

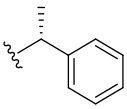
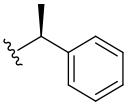


Scheme 107

Using these two sets of conditions the *N*-Boc protected sulfamides **4.10** required were synthesised (Table 37). The Burgess intermediate route (method **A**) worked well for the smaller, more nucleophilic amines (Entries 1 and 2) and was carried out on a 0.1 mol scale in the case of **4.4a**, however an excess of the amine is required. Therefore, for more elaborate amines such as enantiopure 1-phenylethylamine, method **B** was preferred (Entries 9 and 10). Subsequent deprotection with trifluoroacetic acid gave the sulfamides **4.4** in good yield.

Table 37

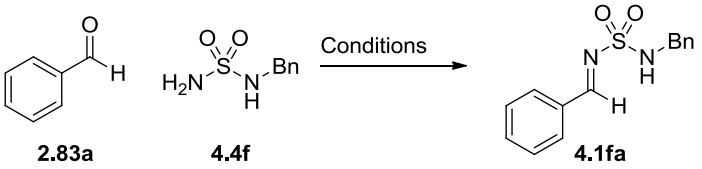


Entry	R		Conditions	4.10 [%]	*N*-Boc-Sulfamide	4.4 [%]	Sulfamide
1	Me	**a**	**A**	82	**4.10a**	83	**4.4a**
2	Et	**b**	**A**	94	**4.10b**	9	**4.4b**
3	Et	**b**	**B**	98	**4.10b**	-	-
4	^{i}Pr	**c**	**A**	63	**4.10c**	70	**4.4c**
5	^{t}Bu	**d**	**A**	89	**4.10d**	95	**4.4d**
6	Ph	**e**	**A**	80	**4.10e**	79	**4.4e**
7	Ph	**e**	**B**	78	**4.10e**	-	-
8	Bn	**g**	**B**	59	**4.10f**	64	**4.4f**
9		**g**	**B**	55	**(*R*)-4.10g**	80	**(*R*)-4.4g**
10		**g**	**B**	58	**(*S*)-4.10g**	73	**(*S*)-4.4g**

4.1.2 Sulfamyl Imine Synthesis

Condensation of *N*-benzylsulfamide **4.4f** with benzaldehyde using the standard *bis*-sulfamyl imine formation conditions (see Section 3.5) gave only a 26% yield (Entry 1, Table 38). However, after a small screen of conditions it was found that employing $Ti(OEt)_4$ as a Lewis acid in THF gave a good yield (Entry 4).

Table 38

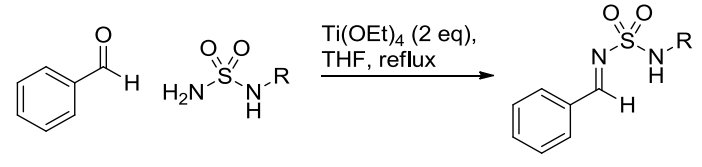


2.83a **4.4f** **4.1fa**

Entry	Conditions	Yield **4.1fa** [%]
1	Amberlyst 15®, benzene, reflux, Dean-Stark	26
2	$MgSO_4$, PPTS, CH_2Cl_2, rt	trace
3	$CuSO_4$, CH_2Cl_2, rt	trace
4	$Ti(OEt)_4$, THF, reflux	65

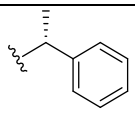
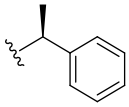
Therefore, the *N*-alkylsulfamides **4.4** in hand were condensed with benzaldehyde to give sulfamyl imines **4.1** in pleasing yields (Table 39). The *N*-methyl sulfamyl imine **4.1aa** was the most attractive substrate for aryl additions at this stage due to its high yielding synthesis, crystallinity and lowest molecular weight.

Table 39



2.83a (1.1 eq) **4.4** **4.1**

Entry	R		Yield [%]	Product[a]
1	Me	**a**	86	**4.1aa**
2	Et	**b**	86	**4.1ba**
3	^{i}Pr	**c**	90	**4.1ca**
4	^{t}Bu	**d**	75	**4.1da**
5	Ph	**e**	85	**4.1ea**
6	Bn	**f**	65	**4.1fa**

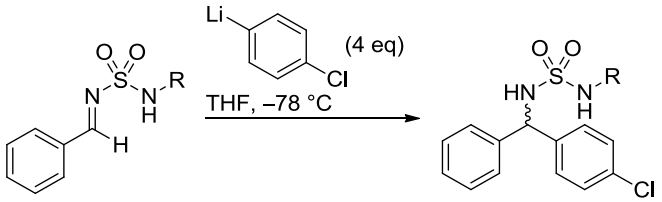
7		**g**	89	**(*R*)-4.1ga**
8		**g**	83	**(*S*)-4.1ga**

[a] Compound labels: first letter refers to R substituent, second letter refers to aryl group from aldehyde.

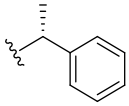
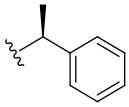
4.1.3 Synthesis of Racemates and Deprotection

It was decided to use 4-chlorobenzene boronic acid as the test substrate for the aryl addition. Therefore, it was necessary to synthesise the racemates of the 4-chlorophenyl addition products. Lithium-halogen exchange of 4-bromochlorobenzene with *n*-butyllithium and addition of the resulting aryllithium species to the imine **4.1** gave the racemic sulfamides **4.2** in good yield (Table 40).

Table 40



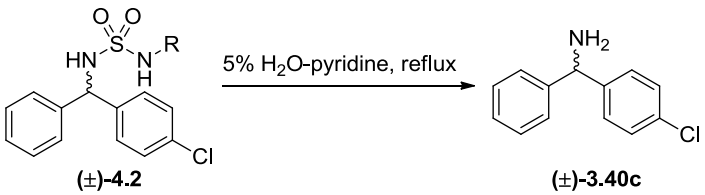
4.1 **(±)-4.2**

Entry	R		Yield [%]	Addition Product[a]
1	Me	**a**	98	**(±)-4.2aab**
2	Et	**b**	74	**(±)-4.2bab**
3	^{i}Pr	**c**	86	**(±)-4.2cab**
4	^{t}Bu	**d**	93	**(±)-4.2dab**
5	Ph	**e**	96	**(±)-4.2eab**
6	Bn	**f**	100	**(±)-4.2fab**
7		**g**	36	**(*R*,±)-4.2gab**
8		**g**	88	**(*S*,±)-4.2gab**

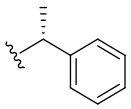
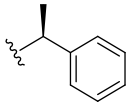
[a] Compound labels: first letter refers to R substituent, second letter refers to aryl group from imine, third refers to aryl group from aryllithium.

The principal reason for the development of these monoalkyl sulfamide addition products was that they would undergo deprotection to the free diarylmethylamines **3.40** under mild conditions, with good recovery and ideally no chromatography. Hence, the racemic addition products **4.2** were subjected to the aqueous pyridine deprotection protocol (see Section 3.4.5) and pleasingly each case gave amine **3.40c** in usable yield (Table 41). It was found that when R was a small alkyl group, the diarylmethylamine **3.40c** was isolated cleanly after the aqueous work-up (Entries 1-4). As would be expected deprotection of **4.2eab**, **4.2fab**, **(*R*)-4.2gab** and **(*S*)-4.2gab** required purification by column chromatography to remove the unwanted amine component (Entries 5-8). Therefore, a small alkyl group was the preferred R group and *N*-methyl sulfamyl imine **4.1aa** was chosen as the substrate for aryl addition optimisation.

Table 41



(±)-4.2 **(±)-3.40c**

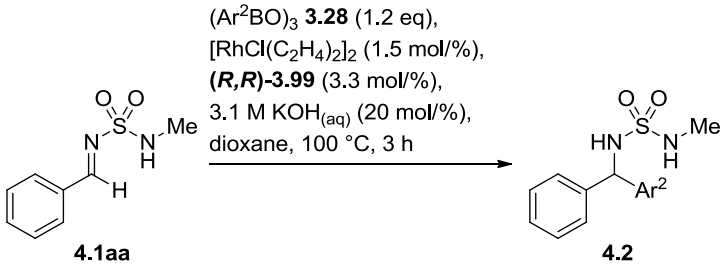
Entry	R	**(±)-3.40c** [%]
1	Me	77
2	Et	84
3	^{i}Pr	87
4	^{t}Bu	79
5	Ph	78[a]
6	Bn	83[a]
7		59[a]
8		72[a]

[a] After column chromatography.

4.2 Optimisation of Aryl Addition to *N*-Methyl-*N*'-[arylmethylidene]sulfamide

The addition of phenyl boroxine **3.28a** to the methyl protected imine **4.1aa** using the previous optimal conditions (see Section 3.4.4.2) gave the addition product in 84% conversion (Entry 1, Table 42). However, when the more electron deficient 4-chlorophenyl boroxine **3.28c** was used the conversion dropped to 32% (Entry 2).

Table 42[a]



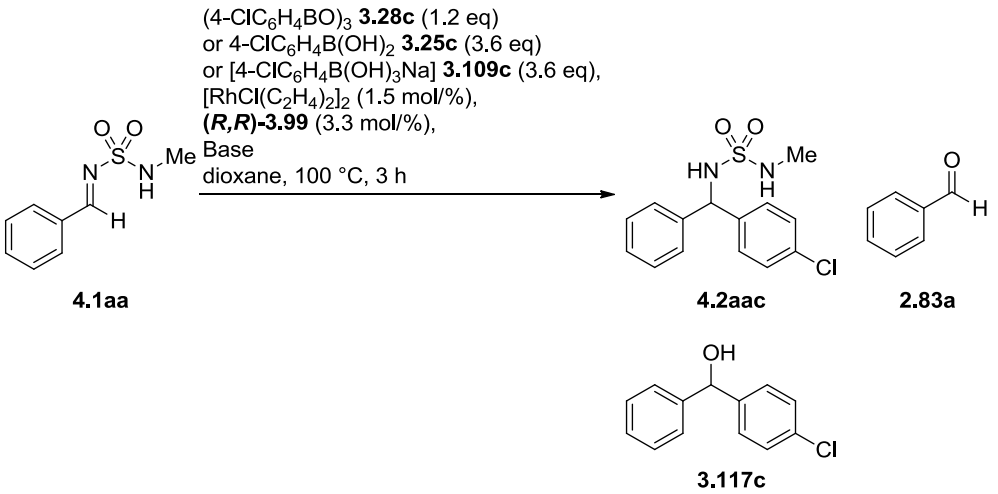
Entry	Ar^2	**4.2** [%][b]	Addition Product
1	Ph	84	**4.2aaa**
2	4-ClC_6H_4	32	**4.2aac**

[a] Reactions were carried out using imine **4.1aa** (0.5 mmol), $(Ar^2BO)_3$ **3.28c** (0.6 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), **(*R,R,R*)-3.99** (3.3 mol/%), base in dioxane (1.6 mL) at 100 °C for 3 h; [b] from crude ^{1}H NMR spectrum.

The main by-product observed was benzaldehyde **2.83a** from hydrolysis of the starting material. Running the aryl boroxine addition reaction with no aqueous base (Entry 1, Table 43) gave no addition product at all. Using only water or more equivalents of aqueous potassium hydroxide with the aryl boroxine **3.28c** did not improve the conversion to addition product (Entries 2 and 4). 4-Chlorophenyl boronic acid **3.25c** alone with no aqueous base also gave no addition product (Entry 5). Addition of boronic acid **3.25c** with 20 mol/% aqueous potassium hydroxide gave a conversion similar to that using 4-chlorophenyl boroxine **3.28c** (Entry 6 vs. 3). Use of aqueous caesium fluoride instead of aqueous potassium hydroxide gave a conversion of 22% with less hydrolysis (Entry 7). The conversion was lower if no water was present (Entry 8). Sodium trihydroxyborate **3.109c** achieved the highest conversion so far when 3.6 equivalents were employed (Entry 9), however, (4-chlorophenyl)(phenyl)methanol **3.117c** was observed in the crude ^{1}H NMR spectrum (presumably from aryl addition to benzaldehyde from

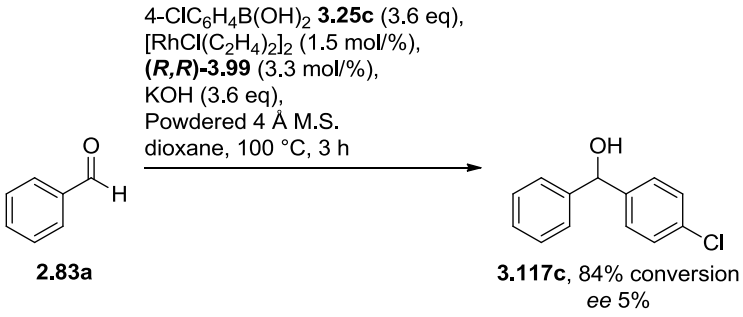
imine hydrolysis). The rhodium catalysed addition of 4-chlorophenyl boronic acid to benzaldehyde **2.83a** was carried out with a good conversion of 84% into alcohol **3.117c**, however minimal enantioselectivity was achieved (Scheme 108).

Table 43[a]



Entry	Boron Species	Base	Eq	Additive	**4.2aac** [%][b]	**4.1aa** [%][b]	**2.83a** [%][b]	**3.117c** [%][b]
1	**3.28c**	-	-	-	0	79	21	0
2	**3.28c**	-	-	H_2O[d]	16	31	53	0
3	**3.28c**	KOH	0.2	H_2O[d]	32	26	42	0
4	**3.28c**	KOH	3.6	H_2O[d]	0	0	100	0
5	**3.25c**	-	-	-	0	44	56	0
6	**3.25c**	KOH	0.2	H_2O[d]	28	44	28	0
7	**3.25c**	CsF	0.2	H_2O[d]	22	65	13	0
8	**3.25c**	CsF	0.2	-	16	54	30	0
9	**3.109c**	-	-	-	73	1	4	22

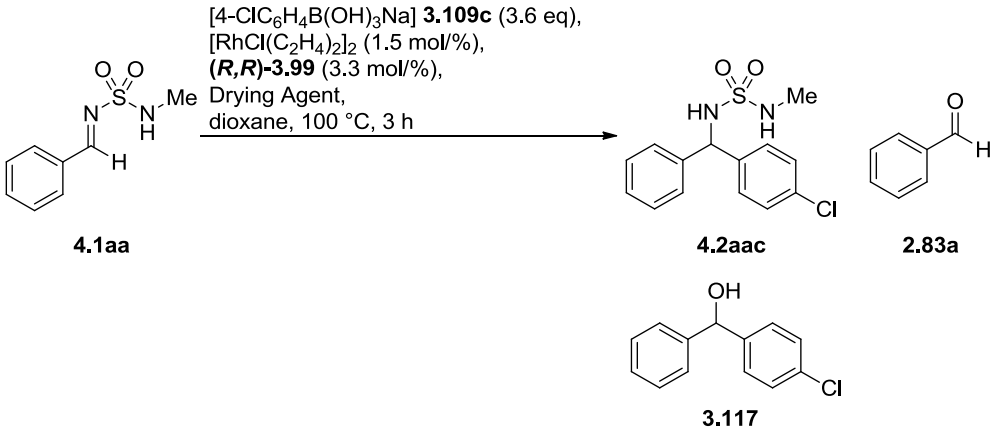
[a] Reactions were carried out using imine **4.1aa** (0.5 mmol), (4-$ClC_6H_4BO)_3$ **3.28c** (0.6 mmol), [4-$ClC_6H_4B(OH)_3Na$] **3.109c** (1.8 mmol) or 4-$ClC_6H_4B(OH)_2$ **3.25c** (1.8 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), ***(R,R,R)*-3.99** (3.3 mol/%) and base in dioxane (1.6 mL) at 100 °C for 3 h; [b] from crude ^{1}H NMR spectrum; [c] 20 mol/%; [d] 1.8 mmol; [e] 300 mg.



Scheme 108

Encouraged by the imine result (Entry 9, Table 43), the addition of sodium trihydroxyborate **3.109c** was repeated with a variety of dehydrating agents with the aim of preventing hydrolysis (Table 44). However, in all cases this was unsuccessful. A range of other aryl boron species was screened however, no improvement was seen (Table 45).

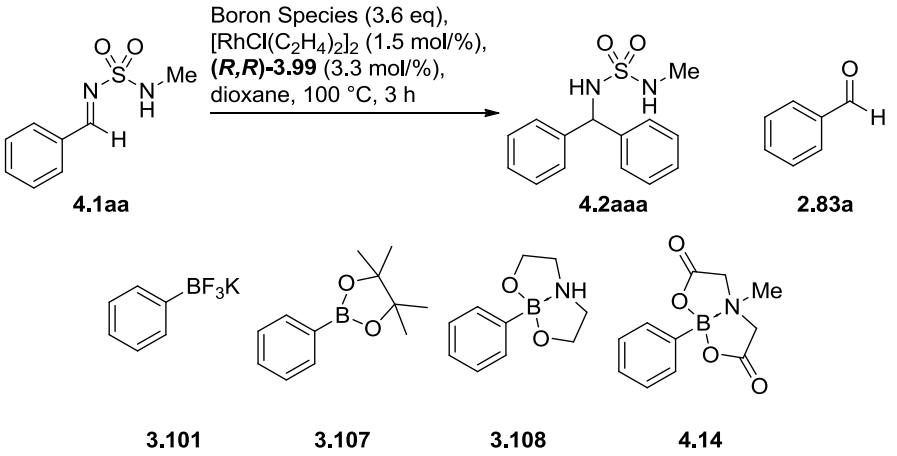
Table 44[a]



Entry	Drying Agent	**4.2aac** [%][b]	**4.1aa** [%][b]	**2.83a** [%][b]	**3.117c** [%][b]
1	Powdered 4 Å M.S.[c]	0	3	70	27
2	4 Å M.S[c]	0	12	61	27
3	$MgSO_4$[c]	0	16	78	6
4	$Ti(OEt)_4$[d]	2	10	79	8

[a] Reactions were carried out using imine **4.1aa** (0.5 mmol), [4-$ClC_6H_4B(OH)_3Na$] **3.109c** (1.8 mmol), [$RhCl(C_2H_4)_2]_2$ (1.5 mol/%), **(*R,R,R*)-3.99** (3.3 mol/%) and drying agent in dioxane (1.6 mL) at 100 °C for 3 h; [b] from crude ^1H NMR spectrum; [c] 300 mg; [d] 2 eq, 1.0 mmol.

Table 45[a]

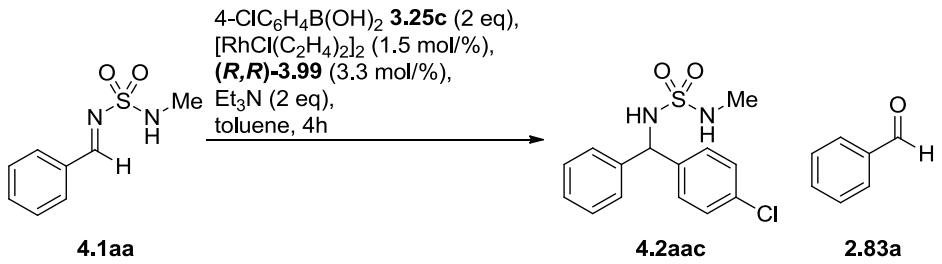


Entry	Boron Species	**4.2aaa** [%][b]	**4.1aa** [%][b]	**2.83a** [%][b]
1	**3.101**	0	96	4
2	**3.107**	0	83	17
3	**3.108**	0	69	31
4	**4.14**	0	46	54

[a] Reactions were carried out using imine **4.1aa** (0.5 mmol), boron species (1.8 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), **(*R,R,R*)-3.99** (3.3 mol/%) in dioxane (1.6 mL) at 100 °C for 3 h; [b] from crude ^{1}H NMR spectrum.

It was decided to investigate other boronic acid additions systems that have been reported. The use of triethylamine in toluene as reported by Lin *et al.*[175] gave a hopeful conversion (Entry 1, Table 46). Increasing the temperature increased the amount of hydrolysis (Entry 2); however, addition of water (Entry 3) improved the conversion to addition product **4.2aac**.

Table 46[a]

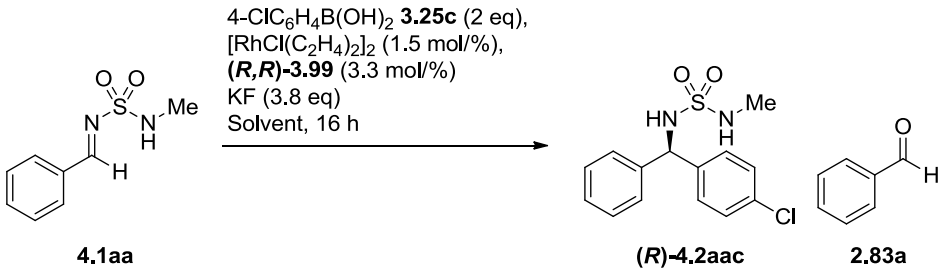


Entry	Additive	*T* [°C]	**4.2aac** [%][b]	**4.1aa** [%][b]	**2.83a** [%][b]
1	-	55	38	35	27
2	-	100	12	29	59
3	H_2O[c]	100	35	12	53

[a] Reactions were carried out using imine **4.1aa** (0.5 mmol), 4-$ClC_6H_4B(OH)_2$ **3.25c** (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), **(*R*,*R*,*R*)-3.99** (3.3 mol/%) in toluene (2 mL) for 4 h; [b] from crude ^{1}H NMR spectrum; [c] 1.8 mmol.

Using the biphasic conditions of Zhou *et al.*[176] gave an excellent yield of sulfamide adduct **4.2aac** with an encouraging enantiomeric excess of 84% (Entry 1, Table 47). The presence of water was found to be critical (Entry 4). Increasing the temperature to 50 °C increased the proportion of hydrolysis product **2.83a** (Entry 2), whilst running the reaction at room temperature impeded the aryl addition reaction (Entry 3). Dichloromethane was found to be as good a solvent as toluene (Entry 5), however solvents that were miscible with water led only to hydrolysis (Entries 6 and 7). Various bases were screened for the addition of boronic acids under these, conditions with CsF, K_3PO_4, K_2CO_3 and Cs_2CO_3 also found to promote the addition (Table 48). The group of Lin have reported a similar rhodium catalysed aryl addition system using KHF_2 (Entry 7, Table 48).[255]

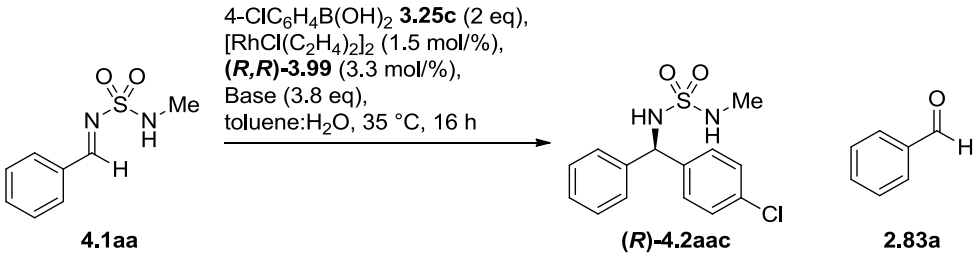
Table 47[a]



Entry	Solvent	*T* [°C]	**(*R*)-4.2aac** [%][b]	**4.1aa** [%][b]	**2.83a** [%][b]	*ee* [%][c]
1	toluene:H_2O	35	84(73)[d]	1	15	84 (*R*)
2	toluene:H_2O	50	42	0	58	-
3	toluene:H_2O	rt	50	7	43	-
4	toluene	35	35	12	53	-
5	CH_2Cl_2:H_2O	35	87(79)[d]	0	13	85 (*R*)
6	dioxane:H_2O	35	0	0	100	-
7	DMF: H_2O	35	0	0	100	-

[a] Reactions were carried out using imine **4.1aa** (0.5 mmol), 4-$ClC_6H_4B(OH)_2$ **3.25c** (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), **(*R,R,R*)-3.99** (3.3 mol/%) and KF (3.8 eq) in solvent (2 mL) for 16 h; [b] from crude ^{1}H NMR spectrum; [c] determined by chiral HPLC (see Chapter 6: Experimental for conditions); [d] isolated yield in brackets.

Table 48[a]



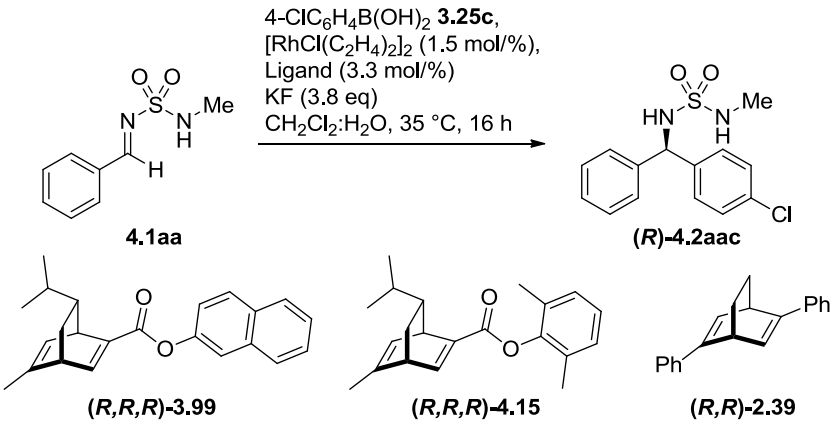
Entry	Base	**(*R*)-4.2aac** [%][b]	**4.1aa** [%][b]	**2.83a** [%][b]
1	-	13	5	82
2	CsF	70	4	26
3	TBAF	0	0	100

4	KOH	0	0	100
5	Et_3N	0	0	100
6	K_3PO_4	85	0	10
7	KHF_2	57	1	42
8	K_2CO_3	93	1	6
9	Cs_2CO_3	81	0	19

[a] Reactions were carried out using imine **4.1aa** (0.5 mmol), 4-$ClC_6H_4B(OH)_2$ **3.25c** (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), **(*R,R,R*)-3.99** (3.3 mol/%) and KF (3.8 eq) in 1:1 H_2O:toluene (2 mL) for 16 h at 35 °C; [b] from crude ^1H NMR spectrum.

We hoped to improve upon the current enantiomeric excess of 85% (Entry 5, Table 47), therefore a derivative of the current diene ligand **(*R,R,R*)-3.99** was prepared bearing the bulky 2,6-dimethylphenyl group **4.15**.[172] The reaction was run with this bulkier ligand **4.15** and a similar enantiomeric excess was achieved, but with a diminished conversion (Entry 1, Table 49), the solvent system of 1:1 dichloromethane:water was chosen due to the slightly higher enantiomeric excess that the toluene system (Entry 5 *vs.* 1, Table 47). A better result was achieved with Hayashi's (*R*,*R*)-Ph-bod **(*R,R*)-2.39**;[170] this gave an excellent conversion with an improvement in enantiomeric excess (Entry 2, Table 49). (*R*,*R*)-Ph-bod **(*R,R*)-2.39** is commercially available as both enantiomers, but it is expensive (~£100 for 100 mg) as this ligand is made using chiral preparative HPLC to resolved the enantiomers (see Section 3.2.6). Using this ligand **(*R,R*)-2.39** also allowed the number of equivalents of 4-chlorophenyl boronic acid to be reduced to 1.3 eq. with little impact on conversion (Entry 3). This result appears to contradict the findings of Hayashi *et al.*[172] who observed that the rhodium catalysed addition of phenyl boroxine to the nosylimine of 4-chlorobenzaldehyde proceeded at a faster rate with ligand **(*R,R,R*)-3.99** than with (*R*,*R*)-Ph-bod **(*R,R*)-2.39**.

Table 49[a]

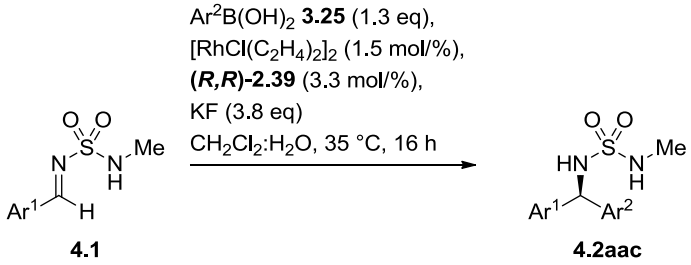


Entry	Ligand	**3.25c** [Eq]	**(*R*)-4.2aac** [%][b]	**4.1aa** [%][b]	**2.83a** [%][b]	*ee* [%][c]
1	**(*R*,*R*,*R*)-4.15**	2	68(67)[d]	3	30	83 (*R*)
2	**(*R*,*R*)-2.39**	2	98(82)[d]	0	2	91 (*R*)
3	**(*R*,*R*)-2.39**	1.3	95(91)[d]	2	4	93 (*R*)

[a] Reactions were carried out using imine **4.1aa** (0.5 mmol), 4-$ClC_6H_4B(OH)_2$ **3.25c** (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), ligand (3.3 mol/%) and KF (3.8 eq) in 1:1 H_2O:CH_2Cl_2 (2 mL) for 16 h at 35 °C; [b] from crude ^1H NMR spectrum; [c] determined by chiral HPLC (see Chapter 6: Experimental for conditions); [d] isolated yield in brackets.

Next, the scope of the reaction was tested with these conditions and it was found that when an electron-withdrawing chloro group was present on the imine, hydrolysis dominated (Entry 2, Table 50).

Table 50[a]



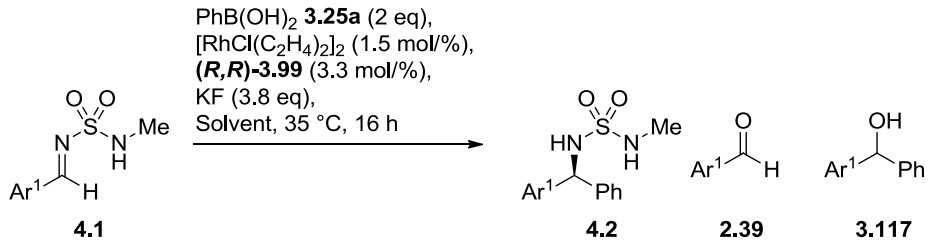
4.1 **4.2aac**

Entry	Ar^1	Ar^2	**4.2aac** [%][b]	**4.1** [%][b]	**2.83** [%][b]
1	Ph	4-ClC_6H_4	95	2	4
2	4-ClC_6H_4	Ph	6	3	92

[a] Reactions were carried out using imine **4.1** (0.5 mmol), $Ar^2B(OH)_2$ **3.25** (0.65 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), **(*R,R*)-2.39** (3.3 mol/%) and KF (3.8 eq) in 1:1 H_2O:CH_2Cl_2 (2 mL) for 16 h at 35 °C; [b] from crude ^{1}H NMR spectrum.

Returning to the previous conditions of **(*R,R,R*)-3.99** as the ligand and two equivalents of boronic acid also showed a fall in conversion to the sulfamide **4.2aac** with an electron-withdrawing group on the imine (Entry 1, Table 51). Alcohol **3.117c** resulting from aryl addition to benzaldehyde was also observed. Use of toluene gave improved conversions over dichloromethane and no alcohol by-product was detected (Entry 1 *vs.* 2). Increasing the catalyst loading to 3 mol/% had no effect (Entry 3). Use of a pH 7.4 buffered aqueous system was detrimental (Entries 4 and 5). The same lowered conversions were achieved when the unsubstituted phenyl boronic acid **3.25a** was added to the unsubstituted imine **4.1aa** (Entries 6 and 7).

Table 51[a]

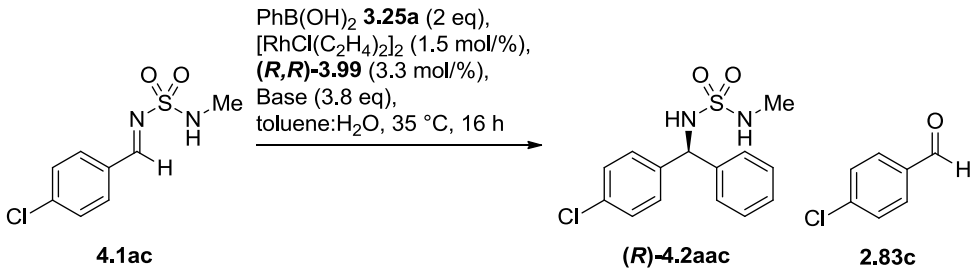


Entry	Ar^1	Solvent	**4.2** [%][b]	Addition Product	**4.1** [%][b]	**2.83** [%][b]	**3.117** [%][b]
1	4-ClC_6H_4	CH_2Cl_2:H_2O	42	**(*S*)-4.2aac**	0	17	41
2	4-ClC_6H_4	toluene:H_2O	66	**(*S*)-4.2aac**	2	32	0
3[d]	4-ClC_6H_4	toluene:H_2O	66	**(*S*)-4.2aac**	5	29	0
4	4-ClC_6H_4	CH_2Cl_2:Buffer[c]	30	**(*S*)-4.2aac**	1	44	25
5	4-ClC_6H_4	toluene:Buffer[c]	57	**(*S*)-4.2aac**	2	38	3
6	Ph	CH_2Cl_2:H_2O	41	**4.2aaa**	1	36	22
7	Ph	toluene:H_2O	54	**4.2aaa**	1	45	0

[a] Reactions were carried out using imine **4.1** (0.5 mmol), $PhB(OH)_2$ **3.25a** (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), **(*R,R,R*)-3.99** (3.3 mol/%) and KF (3.8 eq) in solvent (2 mL) for 16 h at 35 °C; [b] from crude ^1H NMR spectrum; [c] pH 7.4 phosphate buffer; [d] 3 mol/% $[RhCl(C_2H_4)_2]_2$.

The reaction was run at lower temperatures with the aim of slowing the hydrolysis (Entries 1 and 2, Table 52), and possibly running the reaction at 5 °C for an extended reaction time would give reasonable conversion. Varying the base to potassium carbonate gave a good conversion (Entry 4).

Table 52[a]

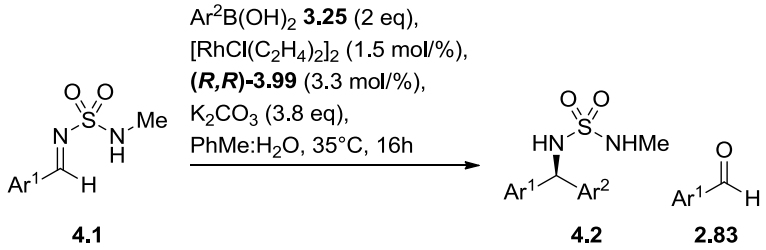


Entry	Base	*T* [°C]	**(*R*)-4.2aac** [%][b]	**4.1ac** [%][a]	**2.83c** [%][a]
1	KF	5	45	44	10
2	KF	rt	39	9	51
3	CsF	35	38	9	53
4	K_2CO_3	35	90	0	7
5	K_3PO_4	35	16	2	82

[a] Reactions were carried out using imine **4.1ac** (0.5 mmol), $PhB(OH)_2$ **3.25a** (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), **(*R,R,R*)-3.99** (3.3 mol/%) and base (3.8 eq) in 1:1 toluene:H_2O (2 mL) for 16 h; [b] from crude ^1H NMR spectrum.

Using potassium carbonate gave good conversions with the electron-withdrawing *para*-chlorine group on the imine (Entry 1, Table 53). However, with no substituent group on the aryl group of the imine mainly hydrolysis was seen (Entry 2).

Table 53[a]



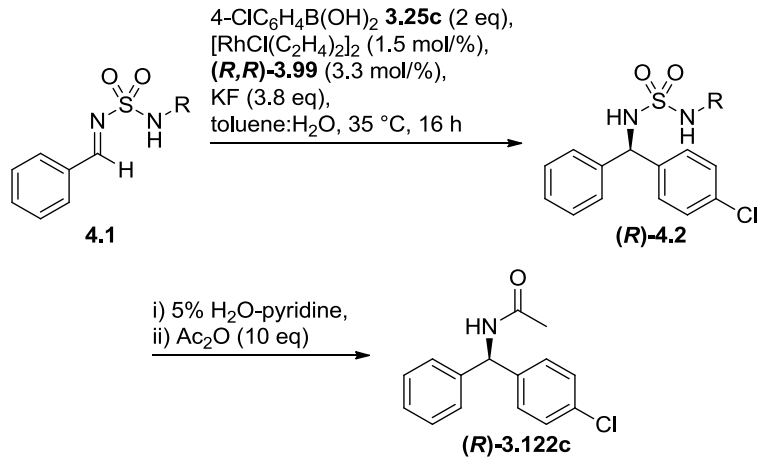
Entry	Ar^1	Ar^2	**4.2** [%][b]	Addition Product	**4.1** [%][b]	**2.83** [%][b]	*ee* [%][c]
1	4-ClC_6H_4	Ph	90(87)[d]	**(*S*)-4.2aac**	0	7	71 (*S*)
2	Ph	Ph	11	**4.2aaa**	1	88	-

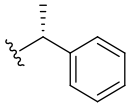
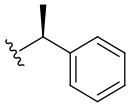
[a] Reactions were carried out using imine **4.1** (0.5 mmol), $Ar^2B(OH)_2$ **3.25** (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), **(*R,R,R*)-3.99** (3.3 mol/%) and K_2CO_3 (3.8 eq) in 1:1 toluene:H_2O (2 mL) for 16 h at 35 °C; [b] from crude ^1H NMR spectrum; [c] determined by chiral HPLC (see Chapter 6: Experimental for conditions); [d] isolated yield in brackets.

4.3 Sulfamyl Imine Scope

Despite extensive optimisation it appeared that the methyl substituted *N*-sulfamyl imine **4.1a** was too prone to hydrolysis to be an effective substrate for our requirements. Therefore it was decided to screen the set of *N*-sulfamylimines **4.1** (Table 39) with the hope that a larger alkyl group would give increased stability and reduced hydrolysis. The effect of the R group on the enantioselectivity of the aryl addition reaction could also be studied.

Table 54[a]



Entry	R	**(*R*)-4.2** [%][b]	Addition Product	*ee* [%][c]	**(*R*)-3.122c** *ee* [%][c]
1	Me	65	**(*R*)-4.2aac**	86	88
2	Et	50	**(*R*)-4.2bac**	87	86
3	^{i}Pr	28	**(*R*)-4.2cac**	86	86
4	^{t}Bu	83	**(*R*)-4.2dac**	86	87
5	Ph	64	**(*R*)-4.2eac**	90	89
6	Bn	61	**(*R*)-4.2fac**	88	89
7		58	**(*R,R*)-4.2gac**	-	83
8		46	**(*S,R*)-4.2gac**	-	85

[a] Reactions were carried out using imine **4.1** (0.5 mmol), 4-$ClC_6H_4B(OH)_2$ **3.25c** (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), **(*R,R,R*)-3.99** (3.3 mol/%) and KF (3.8 eq) in 1:1 toluene:H_2O (2 mL) for 16 h at 35 °C; [b] isolated yield; [c] determined by chiral HPLC (see Chapter 6: Experimental for conditions).

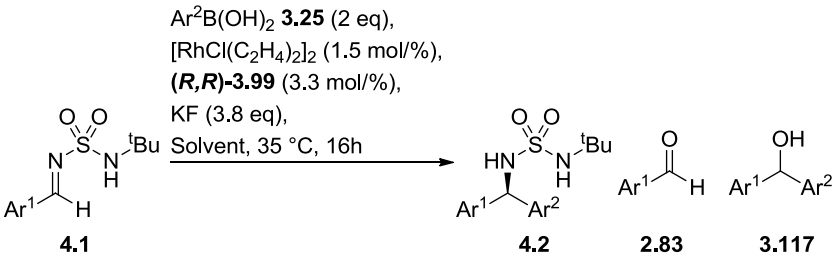
In general, moderate yields of addition product were achieved. The lowest yield was found with the *N-iso*-propylsulfamylimine **4.1ac** (Entry 3, Table 54). The highest yield of addition product was seen with the bulky *tert*-butyl group (Entry 4). This imine, like the methyl analogue **4.1aa**, is an easy to handle, crystalline solid which can be synthesised in high yields and on reasonable scale. It was decided to focus on this *N-tert*-butylsulfamylimine **4.1ad**.

Unfortunately, the size of the alkyl group on the sulfamyl activating group had little effect on the enantioselectivity of the aryl addition. In each case, the enantiomeric excess was confirmed by converting the sulfamide **4.2** to the acetamide **3.122** and measuring its enantiomeric excess as well. A slight increase was seen with the benzyl and phenyl substituents (Entries 5 and 6), but as these require column chromatography to remove the unwanted amine after deprotection we did not want to pursue these substrates. There was little difference between the two enantiomers of imine **4.1ag** (Entries 7 and 8), suggesting that the chiral centre is too far away to exact an influence on the new chiral centre that is being formed.

4.4 Aryl Addition to *N-tert*-Butyl-*N*'-[arylmethylidene]sulfamide

Investigation into the aryl addition to the *tert*-butyl sulfamylimine began by studying the tolerance of and electron-withdrawing substituent on both the electrophilic and nucleophilic components. With the electron-withdrawing 4-chloro substituent the *tert*-butyl imine gave a good conversion to addition product **4.2** (Entry 1, Table 55), and the enantiomeric excess was good at 81%. Again the use of dichloromethane in place of toluene lead to an increase yield of alcohol **3.117** (Entry 2 *vs.* 1). When the substitution was swapped, the addition proceeded much more slowly (Entry 3). As a high percentage of starting material **4.1** remained, the reaction was run for 30 h rather than 16 h, but with no real improvement (Entry 4).

Table 55[a]

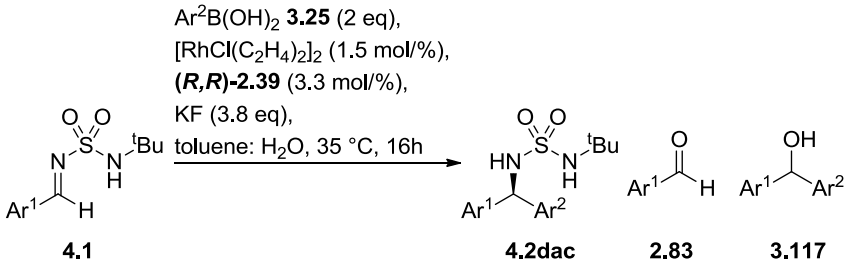


Entry	Ar^1	Ar^2	Solvent	**4.2** [%][b]	**4.1** [%][b]	**2.83** [%][b]	**3.117** [%][b]
1	4-Cl-C_6H_4	Ph	toluene:H_2O	90 (89)[d]	4	7	0
2	4-Cl-C_6H_4	Ph	CH_2Cl_2:H_2O	65	0	15	21
3	Ph	4-Cl-C_6H_4	toluene:H_2O	47	41	13	0
4[e]	Ph	4-Cl-C_6H_4	toluene:H_2O	59	32	8	0
5	Ph	4-Cl-C_6H_4	CH_2Cl_2:H_2O	43	49	8	0
6	Ph	Ph	toluene:H_2O	58	22	20	0

[a] Reactions were carried out using imine **4.1** (0.5 mmol), $Ar^2B(OH)_2$ **3.25** (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), ***(R,R,R)*-3.99** (3.3 mol/%) and KF (3.8 eq) in solvent (2 mL) for 16 h at 35 °C; [b] from crude ^{1}H NMR spectrum; [c] determined by chiral HPLC (see Chapter 6: Experimental for conditions); [d] isolated yield in brackets; [e] reaction time 30 h.

The addition of aryl boronic acids to the *tert*-butyl substituted sulfamyl imine was also tested using the (*R*,*R*)-Ph-bod ***(R,R)*-2.39** ligand (Table 56). The addition of the electron deficient boronic acid **3.25c** gave excellent conversion in both solvent systems (Entries 1 and 3). The enantiomeric excess was improved with (*R*,*R*)-Ph-bod ***(R,R)*-2.39** at 94% rather than 81% with ***(R,R)*-3.99**. In contrast, when the substitution pattern was swapped, hydrolysis dominated (Entries 2 and 4). It was clear that the (*R*,*R*)-Ph-bod ***(R,R)*-2.39** ligand was more sensitive to the electronics of the imine and boronic acid than the other chiral diene ligand ***(R,R)*-3.99**.

Table 56[a]



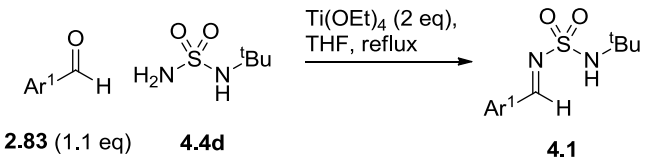
Entry	Ar^1	Ar^2	Solvent	**4.2dac** [%][b]	**4.1** [%][b]	**2.83** [%][b]	**3.117c** [%][b]	*ee* [%][c]
1	Ph	4-Cl-C_6H_4	toluene:H_2O	98(84)[d]	2	0	0	94 (*R*)
2	4-Cl-C_6H_4	Ph	toluene:H_2O	18	10	69	4	-
3	Ph	4-Cl-C_6H_4	CH_2Cl_2:H_2O	93(92)[d]	3	3	0	-
4	4-Cl-C_6H_4	Ph	CH_2Cl_2:H_2O	17	8	75	0	-

[a] Reactions were carried out using imine **4.1** (0.5 mmol), $Ar^2B(OH)_2$ **3.25** (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), **(*R*,*R*)-2.39** (3.3 mol/%) and KF (3.8 eq) in solvent (2 mL) for 16 h at 35 °C; [b] from crude ^{1}H NMR spectrum; [c] determined by chiral HPLC (see Chapter 6: Experimental for conditions); [d] isolated yield in brackets.

4.4.1 Scope of Aryl Addition

It was also evident despite much investigation the current system was unlikely to be optimal for a wide scope of substrates. However, we decided to apply it to a range of substrates to learn about the requirements for this system and the differences between these two ligands. To this end a range of sulfamyl imines bearing a testing variety of electron-withdrawing and donating groups were prepared (Table 57).

Table 57



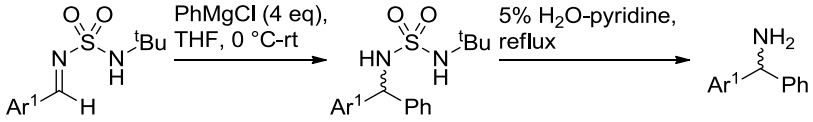
Entry	Ar^1		**4.1** [%]	Product[a]
1	Ph	**a**	75	**4.1da**
2	4-ClC_6H_4	**c**	64	**4.1dc**

3	4-MeC_6H_4	**d**	88	**4.1dd**
4	4-FC_6H_4	**b**	59	**4.1db**
5	3-MeC_6H_4	**h**	76	**4.1dh**
6	3-$MeOC_6H_4$	**k**	89	**4.1dk**
7	4-$CF_3C_6H_4$	**l**	84	**4.1dl**

[a] Compound labels: first letter refers to R substituent, second letter refers to aryl group from aldehyde.

The racemates would also need to be prepared to allow a HPLC assay to be developed. Consequently, phenylmagnesium chloride was added to each imine to give the racemic addition product **4.2** (Table 58). The deprotection conditions of aqueous pyridine were also tested on this series of sulfamides **4.2** and the free amines **3.40** were isolated in good yields.

Table 58



Entry	Ar^1	**(±)-4.2** [%]	Addition Product	**(±)-3.40** [%]	Amine
1	Ph	86[a]	**(±)-4.2daa**	87	**(±)-3.40a**
2	4-ClC_6H_4	93	**(±)-4.2dac**	79	**(±)-3.40c**
3	4-MeC_6H_4	89	**(±)-4.2dad**	78	**(±)-3.40d**
4	4-FC_6H_4	83	**(±)-4.2dab**	88	**(±)-3.40b**
5	3-MeC_6H_4	93	**(±)-4.2dah**	78	**(±)-3.40h**
6	3-$MeOC_6H_4$	83	**(±)-4.2dak**	73	**(±)-3.40k**
7	4-$CF_3C_6H_4$	87	**(±)-4.2dal**	99	**(±)-3.40l**

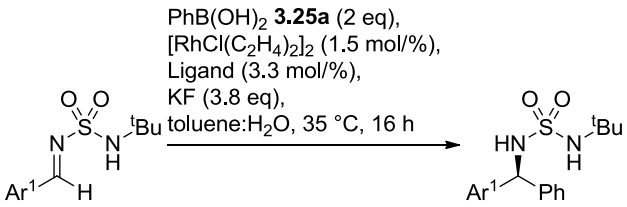
[a] Prepared from **4.30** using method of Borghese *et al.*[222] (see Section 4.5 and Chapter 6 Experimental).

The prepared imines were subjected to the rhodium-catalysed addition of phenyl boronic acid using both ***(R,R,R)*-3.99** and ***(R,R)*-2.39** as the ligand (Table 59). The substitution was then reversed and the substituted aryl boronic acids were added to the sulfamyl imine derived from

benzaldehyde, again using both ligands, the results are shown below in Table 60. Where the conversion was over 40% the sulfamide was isolated and its enantiomeric excess measured. The enantiomeric excesses were confirmed by conversion of the sulfamides **4.2** to the acetamides **3.122**.

In general addition of phenyl boronic acid gave highest conversions with ligand **(*R,R,R*)-3.99** (Entries 3, 5, 7, 9, 11 and 13, Table 59). Only the unsubstituted imine **4.1da** gave a better conversion with **(*R,R*)-2.39** (Entry 1 *vs.* 2). The conversions were highest with the strongly electron-withdrawing groups of 4-chloro- and trifluoromethyl- (Entries 3 and 13). The enantiomeric excesses that were measured were good at 78-86%.

Table 59[a]



4.1 **4.2**

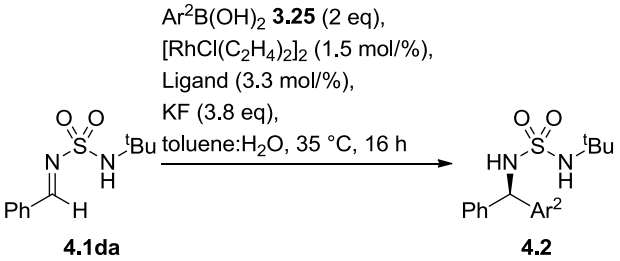
Entry	Ar^1	Ligand	**4.2** [%][b]	Sulfamide	*ee* [%][c]
1	Ph	**(*R,R*)-3.99**	58	**4.2daa**	n/a
2	Ph	**(*R,R*)-2.39**	80(60)[d]	**4.2daa**	n/a
3	4-ClC_6H_4	**(*R,R*)-3.99**	90(89)[d]	**(*S*)-4.2dac**	81 (*S*)
4	4-ClC_6H_4	**(*R,R*)-2.39**	17	**(*S*)-4.2dac**	-
5	4-MeC_6H_4	**(*R,R*)-3.99**	33	**(*S*)-4.2dad**	-
6	4-MeC_6H_4	**(*R,R*)-2.39**	12	**(*S*)-4.2dad**	-
7	4-FC_6H_4	**(*R,R*)-3.99**	45(41)[d]	**(*S*)-4.2dab**	80 (*S*)
8	4-FC_6H_4	**(*R,R*)-2.39**	12	**(*S*)-4.2dab**	-
9	3-MeC_6H_4	**(*R,R*)-3.99**	54(53)[d]	**(*S*)-4.2dah**	85 (*S*)
10	3-MeC_6H_4	**(*R,R*)-2.39**	7	**(*S*)-4.2dah**	-
11	3-$MeOC_6H_4$	**(*R,R*)-3.99**	46(34)[d]	**(*S*)-4.2dak**	86 (*S*)
12	3-$MeOC_6H_4$	**(*R,R*)-2.39**	19	**(*S*)-4.2dak**	-

13	4-$CF_3C_6H_4$	**(*R,R*)-3.99**	86(71)[d]	**(*S*)-4.2dal**	78 (*S*)
14	4-$CF_3C_6H_4$	**(*R,R*)-2.39**	17	**(*S*)-4.2dal**	-

[a] Reactions were carried out using imine **4.1** (0.5 mmol), $PhB(OH)_2$ **3.25** (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), ligand (3.3 mol/%) and KF (3.8 eq) in 1:1 toluene:H_2O (2 mL) for 16 h at 35 °C; [b] from crude ^1H NMR spectrum; [c] determined by chiral HPLC (see Chapter 6: Experimental for conditions); [d] isolated yield in brackets.

The additions of substituted aryl boronic acids to benzaldehyde derived sulfamyl imine **4.1da** had generally higher conversions, than the case with the opposite substitution pattern (Table 59 *vs.* Table 60). Another difference observed was that with the substituted aryl boronic acids, the conversions were in general higher with ligand **(*R,R*)-2.39** (Entries 2, 4, 6, 8, 12 and 14, Table 60) with 3-methylbenzene boronic acid proving the only exception (Entries 9 and 10). The aryl additions with ligand **(*R,R*)-2.39** tolerated electron-donating and electron-withdrawing groups. Ligand **(*R,R*)-2.39** gave excellent enantiomeric excesses 94-98% with the enantiomeric excess being higher than that achieved with ligand **(*R,R,R*)-3.99** in every comparable case.

Table 60[a]



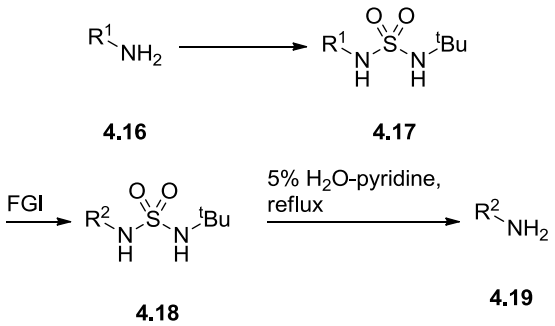
Entry	Ar^2	Ligand	**4.2** [%][b]	Sulfamide	*ee* [%][c]
1	Ph	**(*R,R*)-3.99**	58	**4.2daa**	n/a
2	Ph	**(*R,R*)-2.39**	80(60)[d]	**4.2daa**	n/a
3	4-ClC_6H_4	**(*R,R*)-3.99**	86(83)[d]	**(*R*)-4.2dac**	86 (*R*)
4	4-ClC_6H_4	**(*R,R*)-2.39**	98(84)[d]	**(*R*)-4.2dac**	94 (*R*)
5	4-MeC_6H_4	**(*R,R*)-3.99**	72(68)[d]	**(*R*)-4.2dad**	78 (*R*)
6	4-MeC_6H_4	**(*R,R*)-2.39**	94(71)[d]	**(*R*)-4.2dad**	95 (*R*)
7	4-FC_6H_4	**(*R,R*)-3.99**	53(42)[d]	**(*R*)-4.2dab**	87 (*R*)

8	4-FC_6H_4	**(*R*,*R*)-2.39**	92(90)[d]	**(*R*)-4.2dab**	95 (*R*)
9	3-MeC_6H_4	**(*R*,*R*)-3.99**	43(35)[d]	**(*R*)-4.2dah**	76 (*R*)
10	3-MeC_6H_4	**(*R*,*R*)-2.39**	7	**(*R*)-4.2dah**	-
11	3-$MeOC_6H_4$	**(*R*,*R*)-3.99**	51(37)[d]	**(*R*)-4.2dak**	84 (*R*)
12	3-$MeOC_6H_4$	**(*R*,*R*)-2.39**	93(91)[d]	**(*R*)-4.2dak**	97 (*R*)
13	4-$CF_3C_6H_4$	**(*R*,*R*)-3.99**	46(32)[d]	**(*R*)-4.2dal**	90 (*R*)
14	4-$CF_3C_6H_4$	**(*R*,*R*)-2.39**	94(84)[d]	**(*R*)-4.2dal**	98 (*R*)

[a] Reactions were carried out using imine **4.1** (0.5 mmol), $PhB(OH)_2$ **3.25** (1.0 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol/%), ligand (3.3 mol/%) and KF (3.8 eq) in 1:1 toluene:H_2O (2 mL) for 16 h at 35 °C; [b] from crude ^{1}H NMR spectrum; [c] determined by chiral HPLC (see Chapter 6: Experimental for conditions); [d] isolated yield in brackets.

In conclusion, a new activating group for imines has been developed namely the *N*-sulfamyl group. The imines can be simply made be condensation of the *N*-alkylsulfamide and arylaldehyde in the presence of a Lewis acid. The *N*-alkylsulfamides can be readily prepared from the appropriate amine and chlorosulfonyl isocyanate in two high yielding steps. Addition of Grignard reagents to these activated imines gives racemic sulfamides in good yield. Rhodium catalysed addition of aryl boronic acids proceeds in varying yields The optimum yield being achieved with the **(*R*,*R*)-2.39** ligand and the unsubstituted benzaldehyde derived imine **4.1da**. These aryl additions give enantioenriched sulfamides with excellent enantiomeric excess.

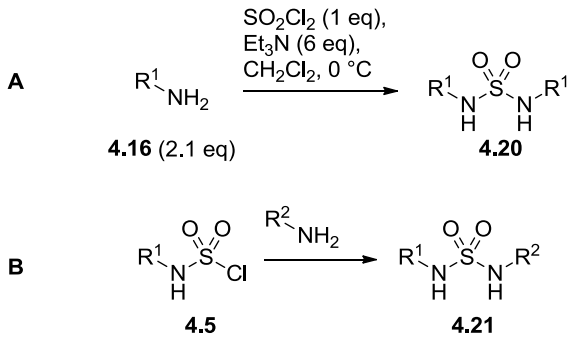
4.5 Sulfamide as a Protecting Group



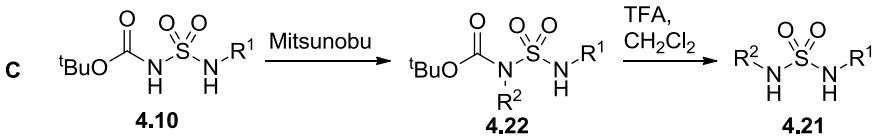
Scheme 109

These sulfamide groups could be used as a general protecting group for amines. If an amine **4.16** (Scheme 109) could be derivatised to the sulfamide **4.17** a functional group interconversion could be carried out on the protected amine to give sulfamide **4.18**. Finally, the amine **4.19** could be isolated using the mild aqueous pyridine conditions. The procedure will be limited to primary amines to maintain the N-H groups in **4.18** required for deprotection. Therefore, methods for the transformation of **4.16** to **4.17** were investigated.

Symmetrical sulfamides **4.20** can be prepared *via* route **A** (Scheme 110) from sulfuryl chloride and two equivalents of the desired amine (as in Section 3.4.3.1).[221] Unsymmetrical sulfamides **4.21** can be prepared from the appropriate *N*-sulfamoyl chloride **4.5** and a primary amine (Route **B**).[242] The synthesis of *N*-sulfamoyl chlorides was discussed in Section 4.1.1 and typically involves hazardous and corrosive reagents.

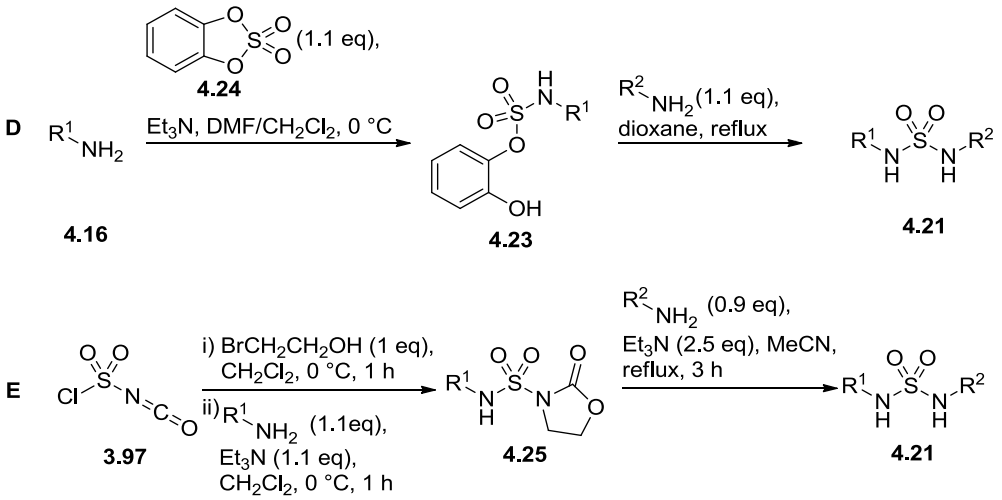


Scheme 110



Scheme 111

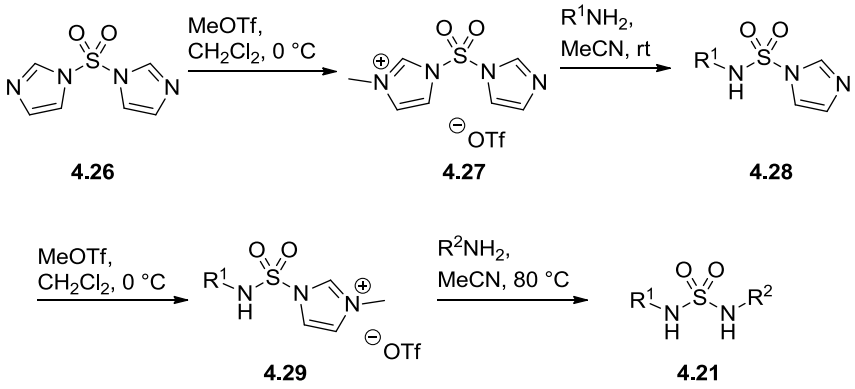
It is possible to elaborate the *N*-Boc-protected sulfamide **4.10** (Section 4.1.1) with a Mitsunobu reaction with an alcohol to give an unsymmetrical sulfamide **4.21** after deprotection (Route **C**, Scheme 111).[221,246] Other routes for the synthesis of unsymmetrical sulfamides require a sulfuryl chloride equivalent with leaving groups that can be displaced sequentially. DuBois found that catechol sulfate **4.24** could be used to synthesise dialkylsulfamide (Route **D**, Scheme 112), however the reaction with anilines proved much slower.[256,257]



Scheme 112

Borghese *et al.* used *N*-sulfamoyloxazolidinones **4.25** prepared from chlorosulfonyl isocyanate **3.97**, displacement of the oxalidinone with a primary amine gave sulfamide **4.21** (Route **E**, Scheme 112).[222] It was found that if a secondary amine was employed, *N*-sulfamoyloxazolidinones **4.25** could be prepared, however the subsequent displacement did not occur.

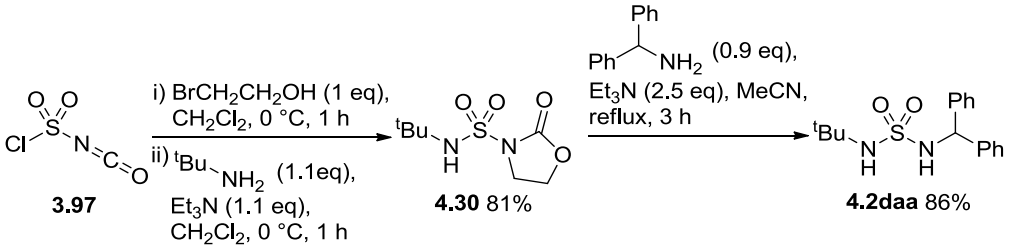
Beaudoin *et al.* looked at using imidazole as a leaving group; alkylation on the nitrogen increases the leaving group ability (Scheme 113).[258] They found that alkylation of *N*,*N*-sulfuryldiimidazole **4.26** with methyl triflate followed by displacement of the imidazolium group with an amine gave intermediate **4.28**. These steps could then be repeated (a higher temperature was required for the second amine displacement) to give the unsymmetrical sulfamide **4.21**.



Scheme 113

The method of Borghese was trialled as it was found that oxalidinone intermediate **4.30** (Scheme 114) could be prepared from *tert*-butylamine in excellent yield. Displacement of the oxalidinone also proceeded in excellent yield to give **4.2daa**, which can be deprotected to the

diarylmethylamine in 87% yield under the standard aqueous pyridine conditions (Entry 1, Table 58).



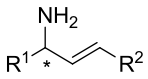
Scheme 114

To conclude a method to introduce a sulfamide group to a primary amine has been found. The use of this protecting group is limited to primary amines as the presence of a free NH is crucial for the subsequent deprotection (see Section 3.4.5). The stability of this group would require further investigation, however in the course of this research it has shown to be stable to refluxing acidic conditions (Entry 2, Table 34) and has been reported to be stable to the strong reducing agent $LiAlH_4$.[207] The possibility of tuning the properties of the group by modifying the R group also provides valuable flexibility.

Chapter 5

5.1 Chiral 1-Aryl-2-propenylamines

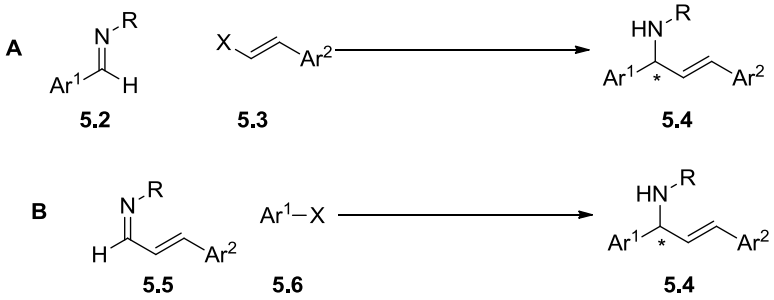
Enantioenriched allylic amines **5.1** (Scheme 115) are useful synthetic building blocks and appear in biologically active natural products.[259,260] The double bond can be oxidised, reduced, or further functionalised to α- and β-amino acids.[261,262]



5.1

Scheme 115

One strategy to synthesise these amines is the addition of an alkenyl reagent **5.3** to an activated aldimine **5.2** (Route **A**, Scheme 116). Alternatively, these allylic amines can be synthesised by the arylation of an activated imine derived from an α,β-unsaturated aldehyde (Route **B**). For both cases a non-racemic amine could be achieved either by the use of a chiral auxiliary in the imine component **5.2/5.5** or by use of a chiral ligand.



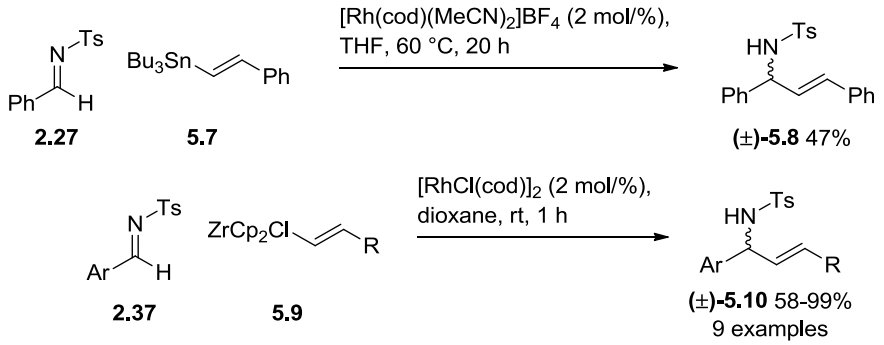
5.2 **5.3** **5.4**

5.5 **5.6** **5.4**

Scheme 116

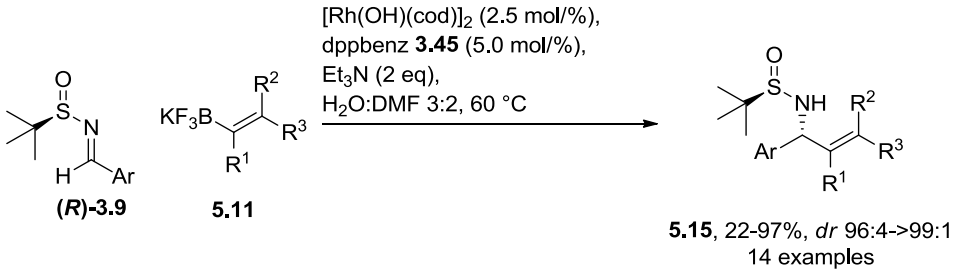
5.1.1 Alkenyl Addition

In 1999, Oi *et al.* reported the first addition of an alkenyl stannane **5.7** to *N*-tosyl imine **2.27**, with rhodium catalysis, to give the racemic allylic amine **(±)-5.8** (Scheme 117).[149] Taguchi, Hanzawa, and co-workers used rhodium catalysed addition of alkenyl zirconocene reagents **5.9** (from hydrozirconation of the appropriate alkyne with the Schwartz reagent) (Scheme 117).[263]



Scheme 117

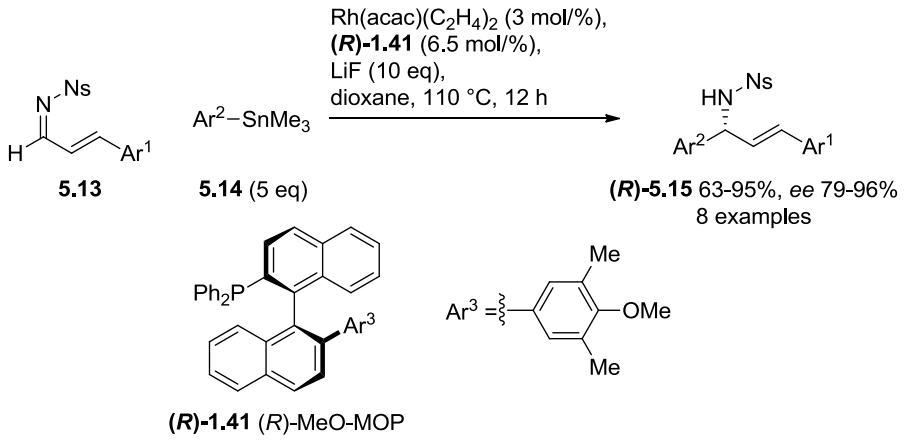
Ellman *et al.* used rhodium catalysis for the diastereoselective addition of alkenyltrifluoroborates to imine **(*R*)-3.9** to give amines **5.12** in excellent diastereomeric ratios (Scheme 118).[264] Alkenyltrifluoroborates are more stable and less prone to hydrolysis than the equivalent alkenyl boronic acids.



Scheme 118

5.1.2 Aryl Addition

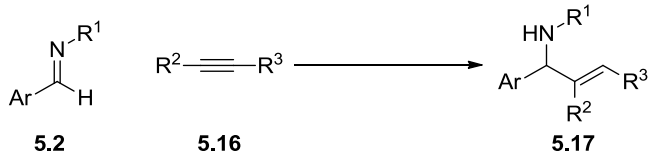
The group of Hayashi reported the use of a stannane, but in this case a trimethylphenyl stannane **5.14** was used to arylate a nosyl protected α,β-unsaturated imine **5.13** (Scheme 119).[151,265] The addition proceeded in a 1,2-fashion with no 1,4-addition product observed. This gave protected allylic amine **(*R*)-5.15** in good yield and excellent enantioselectivity over a range of substrates.



Scheme 119

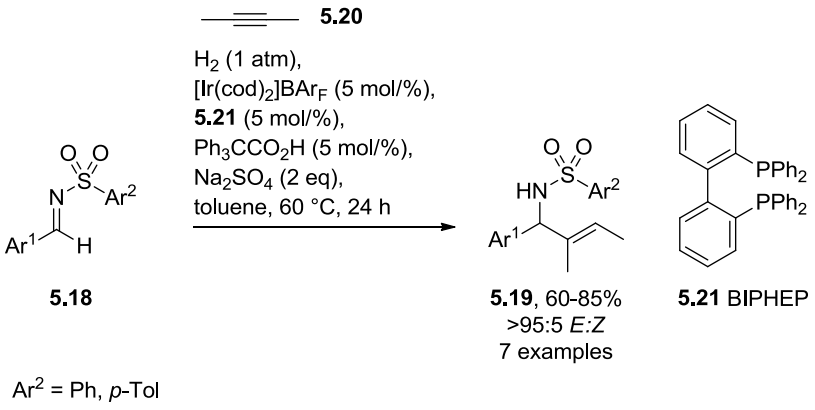
5.1.3 Reductive Coupling of Alkynes

The group of Krische have developed a novel carbon-carbon bonding forming hydrogenation protocol. This allows the coupling of an alkyne **5.16** to an activated imine **5.2** to give the allylic amine **5.17** using iridium catalysis (Scheme 120). The product is equivalent to that of the addition of a vinyl organometallic, but does not require a stoichiometric amount of metal.

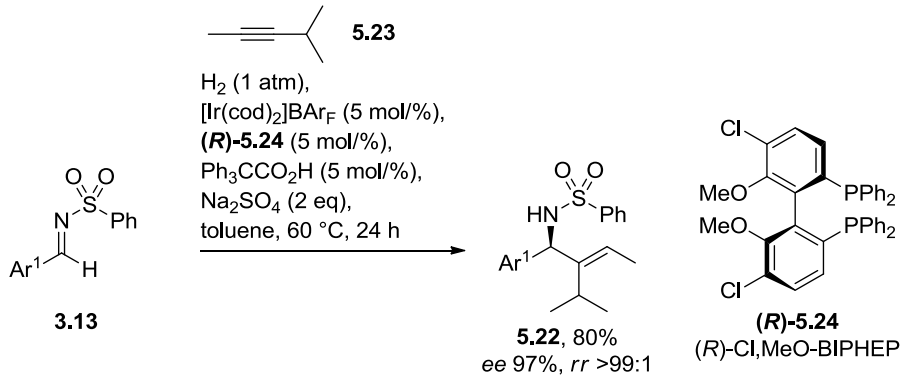


Scheme 120

Using 2-butyne **5.20**, allylic amines **5.21** were made with excellent control over the double bond geometry and no further reduction of the double bond (Scheme 121).[266] It was found necessary to have a carboxylic acid promoter present, in this case Ph_3CCO_2H. If an unsymmetrical alkyne such as 4-methyl-2-pentyne **5.23** were used then the reaction also proceeded with excellent regioselectivity (Scheme 122). Replacing the achiral BIPHEP ligand **5.21** with (*R*)-Cl,MeO-BIPHEP **(*R*)-5.24** gave enantioenriched amines (Scheme 122).[267]



Scheme 121

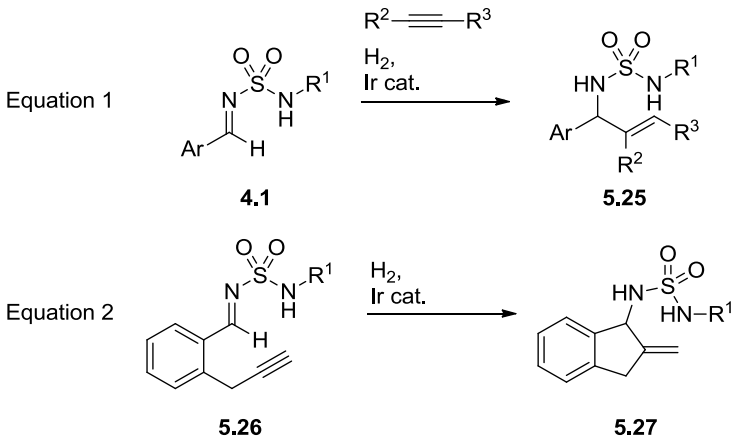


Scheme 122

5.2 Results and Discussion

5.2.1 Aims and Objectives

The aim was to attempt use the newly developed *N*-sulfamyl imines **4.1** (Chapter 4) as a substrate for a reductive alkyne coupling to give to protected allylic amine **5.25** (Equation 1, Scheme 123). It was hoped that the reaction could be optimised through variation of the following parameters: hydrogen pressure, iridium catalyst precursor, ligand, temperature and solvent. Ideally, the reaction would proceed with good regioselectivity and good enantioselectivity if a chiral ligand were employed.



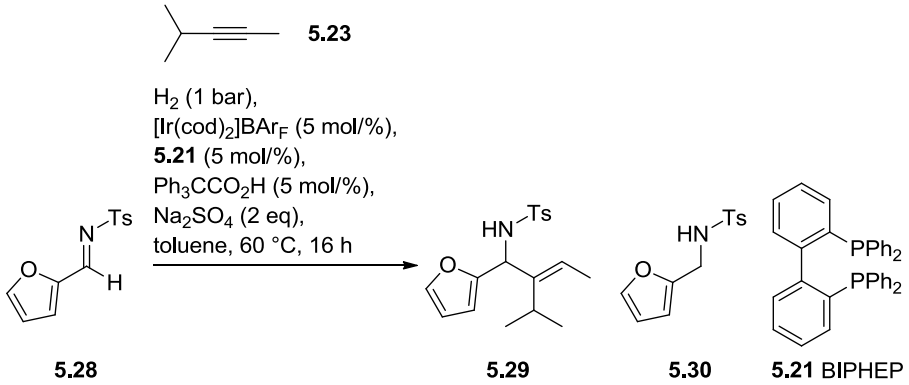
Scheme 123

Secondly, we hoped that an intramolecular reaction using a substrate such as **5.26** could give the bicyclic product **5.27**.

5.2 Intermolecular Reductive Coupling

Initially, *N*-tosyl furaldehyde imine **5.28** and 4-methyl-2-pentyne **5.23** were chosen as the test substrate to try to replicate the results of the Krische group. The achiral BIPHEP **5.21** ligand was used as an alternative to the **(*R*)-5.24**. The reductive coupling reaction product was formed in 34% conversion (Entry 1, Table 61). The mass balance was made up of the sulfamide **5.30**, from reduction of the imine and starting material. An attempt to increase the coupling product by increasing the equivalents of alkyne was unsuccessful giving mainly recovered starting material. It was hypothesised that excess alkyne suppresses the activity of the catalyst.

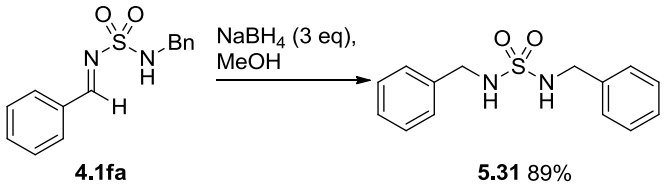
Table 61[a]



Entry	Alkyne [Eq]	**5.29** [%][b]	**5.28** [%][b]	**5.30** [%][b]
1	3	34	31	34
2	30	6	85	9

[a] Reactions were carried out using imine **5.28** (0.2 mmol), 4-methyl-2-pentyne, $[Ir(cod)_2]BAr_F$ (5 mol/%), **5.21** (5 mol/%), Ph_3CCO_2H (5 mol/%) and Na_2SO_4 (0.4 mmol) in toluene (4 mL) under H_2 (1 bar) for 16 h at 60 °C; [b] conversion from crude ^{1}H NMR spectrum.

It was clear some optimisation of the reaction conditions would be required so it was decided to switch to the *N*-sulfamyl imine substrates of interest. At this point, the *N*-sulfamyl imine for which we had an efficient synthesis route in hand was **4.1fa** (Scheme 124). As it was clear that a major side reaction was likely to be reduction, **4.1fa** was treated with sodium borohydride to give the reduced product **5.31** for use as an analytical standard.



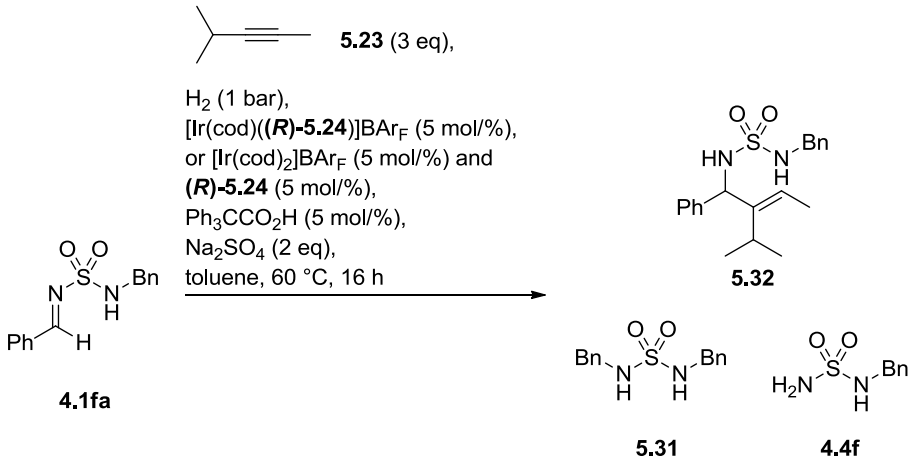
Scheme 124

5.2.1 Optimisation

Firstly, the reductive coupling reaction between **4.1fa** and 4-methyl-2-pentyne was carried out using the optimal conditions of Krische.[266] A conversion to product **5.32** of 15% was observed (Entry 1, Table 62). As expected reduction to sulfamide **5.31** was seen in 38% conversion, another side product observed was primary sulfamide **4.4f**; this must be due to hydrogenolysis

of **5.31**. Only a trace amount of benzaldehyde was observed and no benzyl alcohol therefore hydrolysis of the starting material **4.1fa** is not a major side reaction.

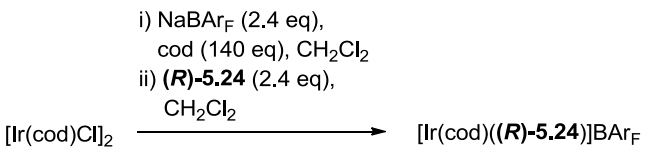
Table 62[a]



Entry	Catalyst	H_2 Uptake [mmol]	**5.32** [%][b]	**4.1fa** [%][b]	**4.4f** [%][b]	**5.31** [%][b]
1	Preformed	0.846	15	8	38	38
2	Formed *in situ*	0.938	15	9	30	46

[a] Reactions were carried out using imine **4.1fa** (0.2 mmol), 4-methyl-2-pentyne (0.6 mmol), [Ir(cod)((***R***)-**5.24**)]BAr_F (5 mol/%) or [Ir(cod)$_2$]BAr_F (5 mol/%) and **(*R*)-5.24** (5 mol/%), Ph_3CCO_2H (5 mol/%) and Na_2SO_4 (0.4 mmol) in toluene (4 mL) under H_2 (1 bar) for 16 h at 60 °C; [b] conversion from crude ^{1}H NMR spectrum.

The initial reaction (Entry 1) had been carried out using the preformed iridium/ligand complex synthesised from [Ir(cod)Cl]$_2$ using the method of Fackler Jnr. *et al.* for the synthesis of similar rhodium complexes with bidentate phosphine ligands (Scheme 125).[268] For the purposes of ligand screening the *in situ* formation of the complex from [Ir(cod)$_2$]BAr_F and ligand would be more practical, so the two approaches were compared. Near identical conversions to product were achieved (Entry 2) with the side reaction of imine reduction being slightly higher.

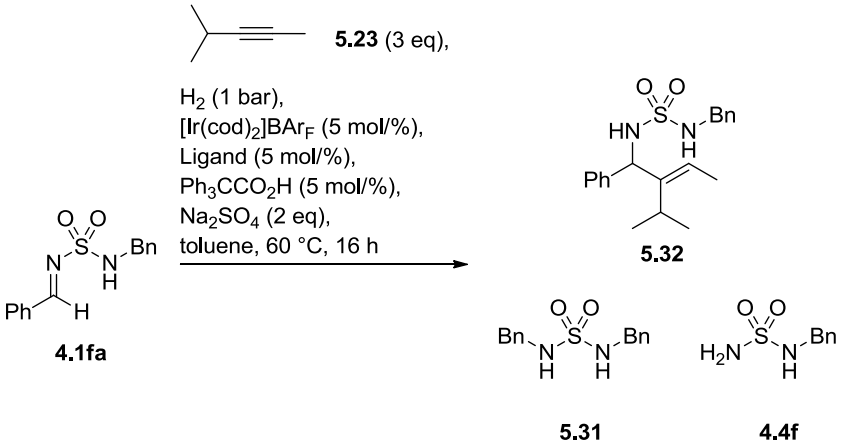


Scheme 125

A variety of ligands (Scheme 126) was tested in the reaction (Table 63). None were found to give better conversions than (*R*)-Cl,MeO-BIPHEP **(*R*)-5.24** (Entry 2). The presence of a ligand is necessary for the reductive coupling (Entry 1). Biaryl systems such as (*R*)-BINAP **(*R*)-1.34**,

(*R*)-SYNPHOS **(*R*)-5.33**, (*R*)-DIFLUORPHOS **(*R*)-5.44**, and CTH-(*R*)-P-PHOS **(*R*)-5.45** gave slightly lower conversions (Entries 3, 4, 18 and 19). (*R*)-Phanephos **(*R*)-2.79**, (*S*,*S*)-Norphos **(*S*,*S*)-5.34**, (*S*,*S*)-Chiraphos **(*S*,*S*)-5.35**, and (*R*)-(*S*)-Josiphos **(*R*,*S*)-5.36** also gave some product (Entries 5-8). CTH-(*R*)-SpiroP **(*R*)-5.39** and (*S*,*S*)-DIOP **(*S*,*S*)-5.42** gave some as yet unidentified side-products.

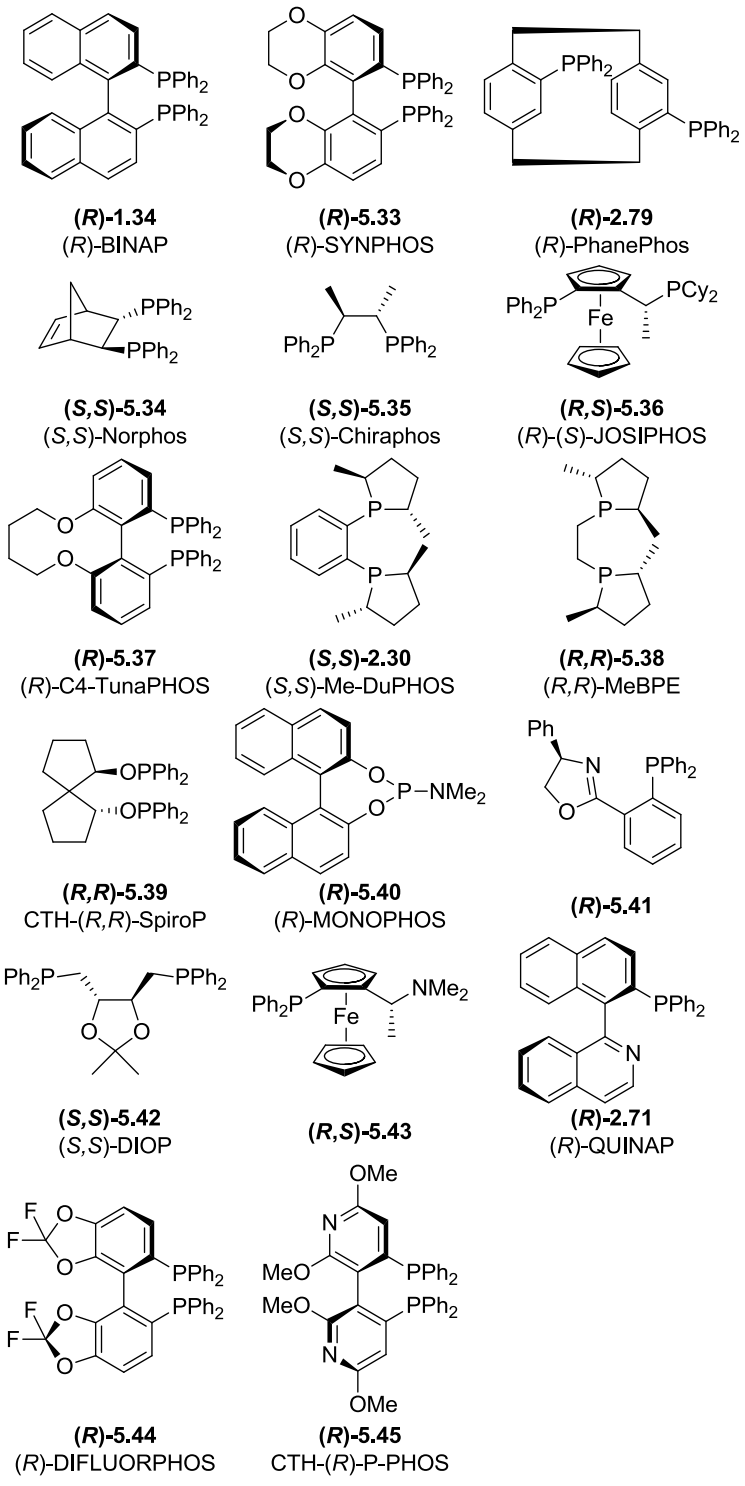
Table 63[a]



Entry	Ligand	H_2 Uptake [mmol]	**5.32** [%][b]	**4.1fa** [%][b]	**4.4f** [%][b]	**5.31** [%][b]
1	no ligand	0.419	0	38	55	7
2	**(*R*)-5.24** (*R*)-Cl,MeO-BIPHEP	1.018	25	0	32	42
3	**(*R*)-1.34** (*R*)-BINAP	1.020	13	5	46	37
4	**(*R*)-5.33** (*R*)-SYNPHOS	1.134	10	0	52	37
5	**(*R*)-2.79** (*R*)-Phanephos	1.056	10	0	9	81
6	**(*S*,*S*)-5.34** (*S*,*S*)-Norphos	1.060	15	0	13	71
7	**(*S*,*S*)-5.35** (*S*,*S*)-Chiraphos	0.848	17	4	47	32
8	**(*R*,*S*)-5.36** (*R*,*S*)-Josiphos	1.251	7	0	5	88
9	**(*R*)-5.37** (*R*)-C4-Tunaphos	0.992	0	34	40	26
10	**(*S*,*S*)-2.30** (*S*,*S*)-MeDUPHOS	0.576	0	13	48	40
11	**(*R*,*R*)-5.38** (*R*,*R*)-MeBPE	0.013	0	53	32	15
12	**(*R*)-5.39** CTH-(*R*)-SpiroP	0.513	0	-	-	-

13	**(*R*)-5.40** (*R*)-MONOPHOS[c]	0.266	0	17	69	14
14	**(*R*)-5.41**	0.272	0	54	37	9
15	**(*S*,*S*)-5.42** (*S*,*S*)-DIOP	0.839	0	-	-	-
16	**(*R*,*S*)-5.43**	0.781	0	68	8	23
17	**(*R*)-2.71** (*R*)-QUINAP	0.324	0	63	20	17
18	**(*R*)-5.44** (*R*)-DIFLUORPHOS	0.663	8	20	64	7
19	**(*R*)-5.45** CTH-(*R*)-P-PHOS	0.830	15	8	56	19
20	PPh_3[c]	0.995	0	0	36	64
21	PCy_3[c]	0.958	0	10	60	30

[a] Reactions were carried out using imine **4.1fa** (0.2 mmol), 4-methyl-2-pentyne (0.6 mmol), $[Ir(cod)_2]BAr_F$ (5 mol/%) and ligand (5 mol/%), Ph_3CCO_2H (5 mol/%) and Na_2SO_4 (0.4 mmol) in toluene (4 mL) under H_2 (1 bar) for 16 h at 60 °C; [b] conversion from crude ^1H NMR spectrum; [c] ligand (10 mol/%) used.



Scheme 126

The reaction was run in a range of solvents; however, in each case unreacted starting material was the major component (Table 64). It was hoped that reducing the pressure would slow the hydrogenation of the starting material and increase the proportion of C-C bond formation. However, the conversion was no better at 0.5 bar, although there was more unreacted starting material remaining (Entry 2, Table 65). Lowering the pressure further gave a lower conversion

still (Entry 3). Varying the temperature had also little effect on the improving the conversion (Table 66).

Table 64[a]

Entry	Solvent	H_2 Uptake [mmol]	**5.32** [%][b]	**4.1fa** [%][b]	**4.4f** [%][b]	**5.31** [%][b]
1	THF	-0.122	0	84	3	13
2	EtOAc	-0.019	0	91	2	6
3	1,2-dichloroethane	0.401	0	37	10	53
4	MeOH	-0.007	0	80	10	11
5	acetone	-0.245	0	90	1	9
6	MeCN	-0.100	0	90	2	8

[a] Reactions were carried out using imine **4.1fa** (0.2 mmol), 4-methyl-2-pentyne (0.6 mmol), [Ir(cod)(**(*R*)-5.24**)]BAr_F (5 mol/%), Ph_3CCO_2H (5 mol/%) and Na_2SO_4 (0.4 mmol) in solvent (4 mL) under H_2 (1 bar) for 16 h at 60 °C; [b] conversion from crude ^{1}H NMR spectrum.

Table 65[a]

Entry	H_2 Pressure [bar]	H_2 Uptake [mmol]	**5.32** [%][b]	**4.1fa** [%][b]	**4.4f** [%][b]	**5.31** [%][b]
1	1.0	0.938	15	9	30	46
2	0.5	0.769	13	27	34	28
3	0.2	-0.002	9	52	35	3

[a] Reactions were carried out using imine **4.1fa** (0.2 mmol), 4-methyl-2-pentyne (0.6 mmol), $[Ir(cod)_2]BAr_F$ (5 mol/%), **(*R*)-5.24** (5 mol/%), Ph_3CCO_2H (5 mol/%) and Na_2SO_4 (0.4 mmol) in toluene (4 mL) under H_2 for 16 h at 60 °C; [b] conversion from crude ^{1}H NMR spectrum.

Table 66[a]

Entry	*T* [°C]	H_2 Uptake [mmol]	**5.32** [%][b]	**4.1fa** [%][b]	**4.4f** [%][b]	**5.31** [%][b]
1	40	1.113	8	5	68	19
2	60	1.166	16	0	39	45
3	80	0.943	15	9	35	41

[a] Reactions were carried out using imine **4.1fa** (0.2 mmol), 4-methyl-2-pentyne (0.6 mmol), $[Ir(cod)_2]BAr_F$ (5 mol/%), **(*R*)-5.24** (5 mol/%), Ph_3CCO_2H (5 mol/%) and Na_2SO_4 (0.4 mmol) in toluene (4 mL) under H_2 (1 bar) for 16 h; [b] conversion from crude ^{1}H NMR spectrum.

The amount of acid promoter present was also varied. It was found that reductive coupling product could still be formed in its absence (Entry 1, Table 67). However, a boost to conversion was achieved if the acid was recrystallised before use (Entry 3). A screen of other acidic additives (Entries 6-9) showed that phenol could promote the reaction just as well as Ph_3CCO_2H (Entry 8).

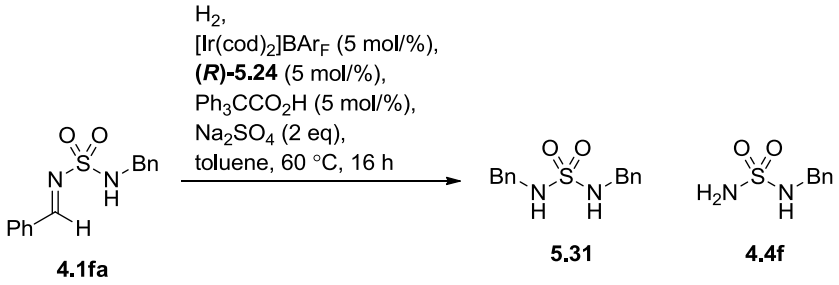
Table 67[a]

Entry	Additive	[mol/%]	H_2 Uptake [mmol]	**5.32** [%][b]	**4.1fa** [%][b]	**4.4f** [%][b]	**5.31** [%][b]
1	Ph_3CCO_2H	0	0.987	11	23	41	24
2	Ph_3CCO_2H	1	1.017	9	10	53	27
3	Ph_3CCO_2H[c]	5	0.711	28	9	24	39
4	Ph_3CCO_2H	10	1.145	6	17	52	24
5	Ph_3CCO_2H	20	0.989	0	21	61	18
6	MeOH	5	1.177	4	0	46	50
7	$3\text{-}NO_2C_6H_4CO_2H$	5	0.902	10	0	49	40
8	PhOH	5	0.829	27	2	27	40
9	TFA	5	1.182	0	0	55	45

[a] Reactions were carried out using imine **4.1fa** (0.2 mmol), 4-methyl-2-pentyne (0.6 mmol), $[Ir(cod)_2]BAr_F$ (5 mol/%), **(*R*)-5.24** (5 mol/%), additive and Na_2SO_4 (0.4 mmol) in toluene (4 mL) under H_2 (1 bar) for 16 h at 60 °C; [b] conversion from crude ^{1}H NMR spectrum, [c] acid recrystallised from methanol prior to use.

The substrates were subjected to the reductive coupling conditions to assess their stability. After 16 h with a hydrogen pressure of 1 bar, no imine **4.1fa** remained with major product being the reduced sulfamide **5.31** and an appreciable amount of hydrogenolysis to the primary sulfamide **4.4f** (Entry 1, Table 68). With no hydrogen present, imine was recovered after 16 h with 44% **4.4f** this time presumably for hydrolysis of the imine.

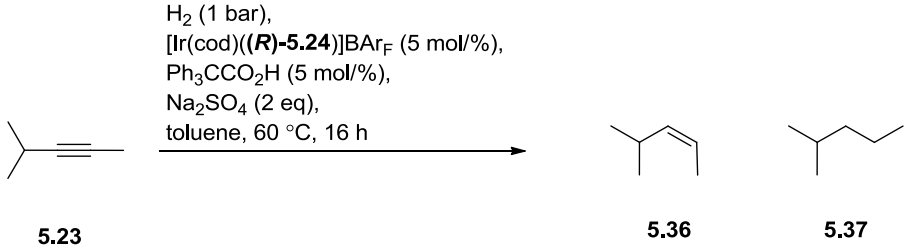
Table 68[a]



Entry	H_2 Pressure [bar]	H_2 Uptake [mmol]	**4.1fa** [%][b]	**4.4f** [%][b]	**5.31** [%][b]
1	1	0.140	0	21	78
2	0	0.000	56	44	0

[a] Reactions were carried out using imine **4.1fa** (0.2 mmol), [Ir(cod)((***R***)-**5.24**)]BAr_F (5 mol/%), Ph_3CCO_2H (5 mol/%) and Na_2SO_4 (0.4 mmol) in solvent (4 mL) under H_2 for 16 h at 60 °C; [b] conversion from crude ^{1}H NMR spectrum.

When the alkyne **5.23** alone was subjected to the reductive coupling conditions, hydrogen uptake was still recorded indicting reduction of the alkyne. The reductive coupling with imine **4.1fa** was repeated using d_6-benzene as the solvent, the resulting ^{1}H NMR spectrum showed the presence of the *cis*-alkene **5.36** (Scheme 127). However, in the absence of the imine substrate alkane **5.37** is observed by ^{1}H NMR after 16 h. If the reaction is stopped after 2 h alkene **5.36** is observed. Hydrogenation of the alkyne **5.23** was found to be more rapid than hydrogenation of the imine **4.1fa**.

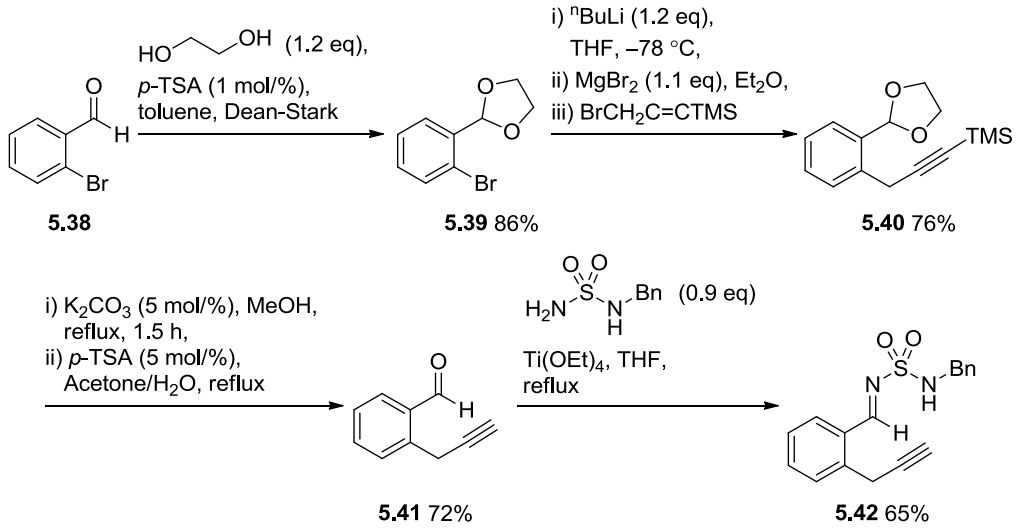


Scheme 127

Increasing the catalyst loading with the aim of increasing conversion to **5.32** was not investigated as the current loading of 5 mol/% was already thought to be high. Despite extensive optimisation the conversion to **5.32** could not be improved from a disappointing 28%; a similar conversion was observed with Krische's own substrates (Table 61). As a result, no enantiomeric excesses were determined for these reactions. The competition of side reactions in the form of imine and alkyne reduction could not be worked around.

5.2.3 Intramolecular Reductive Coupling

5.2.3.1 Synthesis of Substrate



5.38 **5.39** 86% **5.40** 76%

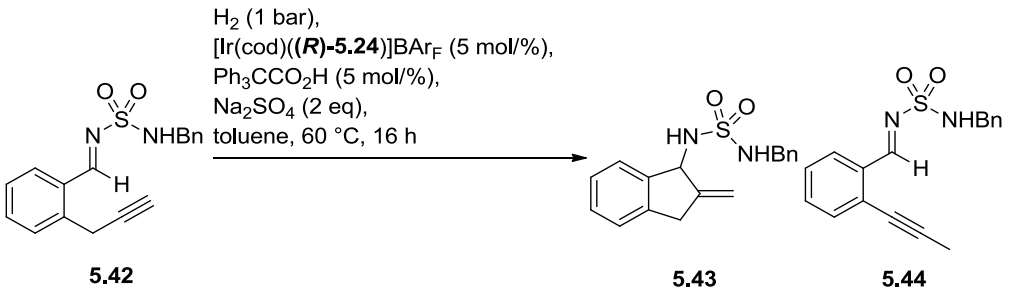
5.41 72% **5.42** 65%

Scheme 128

First, the aldehyde was protected as acetal **5.39** (Scheme 128), the Grignard reagent was formed and coupled to give **5.40** in good yield. Deprotection of the acetal and TMS groups were carried out without isolation of the intermediate to give aldehyde **5.41**. This was then coupled with the sulfamide **4.4f** to yield the substrate **5.42**.

5.2.3.2 Intramolecular Reductive Coupling

Unfortunately, when exposed to the coupling conditions, no hydrogen uptake was recorded and no desired product was observed in the crude ^{1}H NMR spectrum. The one isolated side product appears to be the isomerised alkyne **5.44** (Scheme 129**)**.



5.42 **5.43** **5.44**

Scheme 129

Chapter 6 Experimental

All experiments were carried out under an argon atmosphere using standard Schlenk techniques. Solvents were dried prior to use: THF, diethyl ether, DME and dioxane were distilled from sodium-benzophenone ketyl and dichloromethane from calcium hydride. Proton, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded on Bruker DPX400, Bruker AV400 and Bruker AV(III)400 spectrometers using Me_4Si or residual solvent as an internal reference. ^{19}F NMR spectra for compounds **3.100b**, ***meso*-3.100b**, **(*R*,*R*)-3.100b** and **(*S*,*S*)-3.100b** were referenced to TFE at −77.4 ppm. All *J* values are in Hz. Infrared spectra were recorded on a Bruker Tensor 27 machine. Mass spectra were recorded using Electrospray (ES) or electron impact (EI) techniques using a Bruker ApexIV FT-ICR machine. Optical rotations were measured using a Bellingham Stanley ADP440 digital polarimeter at ambient temperature in units of 10^{-1} ° cm^2 g^{-1} (*c* in g/100 mL). Diastereoselectivities and enantioselectivities were determined by chiral HPLC and chiral GC. HPLC analyses were performed on a Varian Prostar System using Daicel columns under the conditions given. GC analyses were performed on a Varian 430 gas chromatograph using a CP-ChiraSil-Dex CB column under the conditions given. Thin layer chromatography (TLC) was performed on Merck silica gel 60 $F_{254+366}$ pre-coated plates (0.25 mm) silica. The plates were visualised by the use of a combination of ultraviolet light (254 and 366 nm) and/or aqueous potassium permanganate with heating. Liquid chromatography was by forced flow (flash chromatography) with the solvent systems indicated using silica gel 60 (220-240 mesh) supplied by Fluka.

6.1 General Methods

General Method A: *N*-Diphenylphosphinoyl Imine 2.20 Preparation[110,111]

Titanium tetrachloride (5.0 mmol, 0.5 eq) in CH_2Cl_2 (4 mL) was added dropwise to a stirred solution of the aldehyde (10.0 mmol, 1 eq), diphenylphosphinic amide (10.0 mmol, 1 eq) and triethylamine (35.0 mmol, 3.5 eq) in CH_2Cl_2 (50 mL) at 0 °C. The solution was stirred at 0 °C for 1 h and room temperature for 1 h. The suspension was filtered through a silica pad, washed with 1:1 CH_2Cl_2:EtOAc. The filtrate was concentrated to a cream solid and purified by flash

chromatography (1:1 CH_2Cl_2:EtOAc). Imines **2.20a-k** were prepared by Samir El Hajjaji.[106,269]

General Method B: Racemic Methylation of *N*-Diphenylphosphinoyl Imines 2.20

A flame dried Schlenk tube was charged with imine **2.20** (0.6 mmol, 1 eq) in dried Et_2O (10 mL). The suspension was cooled to 0 °C, a minimum amount of CH_2Cl_2 was added (~5 mL) to dissolve the compound. Methylmagnesium bromide (3.0 M in Et_2O solution, 0.6 mL, 1.8 mmol, 3 eq) was slowly added to the solution. The reaction mixture was stirred first at 0 °C for 30 min and then at room temperature for 1 h after which time it was quenched at 0 °C with water (10 mL). The product was extracted into CH_2Cl_2 (3 × 20 mL), the combined organic extracts were washed successively with water (20 mL) and brine (20 mL), dried (Na_2SO_4) and the solvent removed *in vacuo* to afford the crude amine. Purification by flash chromatography (EtOAc) gave the pure protected secondary amines **(±)-2.21**.

General Method C: Enantioselective Methylation of *N*-Diphenylphosphinoyl Imines 2.20

A flame-dried Schlenk tube was charged with $[RhCl(C_2H_4)_2]_2$ (6.8 mg, 2.9 mol/%), (*R,R*)-MeDuPHOS **(*R,R*)-2.30** (19.1 mg, 10.4 mol/%) and THF (6 mL). The solution was stirred at room temperature for 30 min before the imine **2.20** (0.6 mmol, 1 eq) in THF (4 mL) was added. After a further 5 min dimethylzinc (2.0 M in toluene, 0.6 mL, 1.2 mmol, 2 eq) was added dropwise. The reaction mixture was stirred at reflux for 3 h, then quenched with sat. NH_4Cl solution (20 mL), extracted with CH_2Cl_2 (3 × 20 mL). The organics were dried (Na_2SO_4) and concentrated *in vacuo* to an oil, which was purified using flash chromatography (EtOAc).

General Method D: Protecting Group Exchange – Conversion of 2.21 into Trifluoroacyl or Acyl Derivatives 2.93

A 10 mL vial equipped with a magnetic stirrer was charged with the pure protected secondary amine **2.21** (30 mg) and trifluoroacetic anhydride (50 eq) or acetyl chloride (50 eq) with DMAP (7 mol/%). The suspension was stirred for 30 min before the cautious addition of 2

drops of water. The resulting solution was stirred overnight and the reaction mixture was transferred in a larger container before quenching it cautiously with sat. $NaHCO_3$ solution (30 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL), dried (Na_2SO_4) and concentrated. The residue was purified by filtration over a pad of silica (CH_2Cl_2) or by flash chromatography (1:1 pet. ether:EtOAc). Samples of **2.93**, assessed pure by ^1H NMR spectroscopy, were used directly for *ee* determination by GC. Assays were carried out on an autosampler equipped Varian 430 using the conditions and columns described in Table 69.

General Method E: *Bis*-Sulfamyl Imine 3.85 Preparation

A suspension of sulfamide (25 mmol, 1 eq), aldehyde (50 mmol, 2 eq) and Amberlyst® 15 (0.3 g) in benzene (60 mL) was refluxed overnight using a Dean-Stark trap. The reaction mixture was allowed to cool, CH_2Cl_2 (50 mL) was added, the Amberlyst® 15 was removed by filtration.

General Method F: Aryl Boroxine 3.28 Preparation

A suspension of the aryl boronic acid **3.25** in benzene/toluene (50 mL) was stirred at reflux for 6-18 h with a Dean-Stark trap. After cooling the resulting white precipitate was collected by filtration and washed with hexanes (in some cases a second crop could be obtained from the filtrate) the boroxines **3.28** were obtained in quantitative yield (5-15% boronic acid remaining).

General Method G: Aryl Grignard Reagent Addition to *Bis*-Sulfamyl Imines 3.85

A flame dried Schlenk was charged with the imine **3.85** (0.75 mmol, 1 eq), and Et_2O (10 mL) and cooled to 0 °C. Arylmagnesium bromide (3.00 mmol, 4 eq) was added dropwise with stirring at 0 °C. The solution was stirred 4-18 h and allowed to warm to rt. The reaction mixture was then quenched with sat. NH_4Cl solution (20 mL), extracted with Et_2O (2 × 20 mL), the organics were dried (Na_2SO_4) and concentrated.

General Method H: Rhodium Catalysed Aryl Boroxine 3.28 Addition to *Bis*-Sulfamyl Imines 3.85

A flame dried Schlenk was charged with $[RhCl(C_2H_4)_2]_2$ (2.9 mg, 7.5 µmol, 3 mol/%), **(*R,R,R*)-3.99** (5.5 mg, 16.5 µmol, 6.6 mol/%) and dioxane (0.4 mL), the orange solution was stirred at rt for 10 min. Imine **3.85** (0.25 mmol, 1 eq), aryl boroxine **3.28** (0.6 mmol, 2.4 eq), 3.1 M $KOH_{(aq)}$ (32.2 µL, 40 mol/%) and dioxane (1.2 mL) were added. The yellow solution was stirred at 100 °C for 3 h and became dark brown. The mixture was filtered through a pad of silica, flushed with Et_2O (20 mL), the filtrate was concentrated and purified by column chromatography.

General Method I: Deprotection of 3.100 and 4.2 to Free Diarylmethylamines 3.40

A solution of the sulfamide **3.100/4.2** in 5% H_2O-pyridine (10 mL) was stirred at reflux overnight. The pyridine was removed *in vacuo* and the residue was partitioned between 1 M HCl (20 mL) and Et_2O (20 mL). The aqueous layer was basified with 2 M NaOH and extracted with Et_2O (2 × 15 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated to give the product with no further purification necessary. In the cases of **4.2** where R = Ph, Bn, $CH(CH_3)Ph$ column chromatography was required (1:1 pet. ether:EtOAc).

General Method J: Acetylation of Free Diarylmethylamines 3.40

Acetyl chloride (1.1 eq) was added to a stirred solution of the amine **3.40** (1 eq) and pyridine (2 eq) in CH_2Cl_2 or $CHCl_3$ (2 mL). The solution was stirred at rt for 4-18 h. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) washed with sat. $NaHCO_3$ solution (15 mL) and 2 M HCl (15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give the product.

General Method K: Deprotection and Acetylation

A solution of the sulfamide **3.100** in 5% H_2O-pyridine (10 mL) was stirred at reflux overnight. The solution was allowed to cool and acetic anhydride (10 eq) was added, stirred at rt for 7 h. Then 1 M HCl (20 mL) was added, the mixture was extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with 2 M HCl (2 × 20 mL), H_2O (20 mL) and brine

(20 mL) then dried (Na_2SO_4) and concentrated to give the product with no further purification necessary.

General Method L: Synthesis of *tert*-Butyl *N*-alkylsulfamoylcarbamate 4.10

Chlorosulfonyl isocyanate (8.7 mL, 0.1 mol, 1 eq) in toluene (10 mL) was added dropwise to a stirred solution of *tert*-butanol (9.4 mL, 0.1 mol, 1 eq) in toluene (100 mL) at 3 °C over 30 min. The colourless suspension was stirred at 3 °C for 45 min, then pyridine (17.7 mL, 0.22 mol, 2.2 eq) was added dropwise over 15 min and the suspension stirred at 7 °C for 60 min. Primary amine (40-70 wt. % in H_2O, 0.6 mol, 6 eq) was added dropwise at 5 °C over 30 min and the biphasic mixture was stirred for 2 hr at 5 °C. The layers were separated, the aqueous was washed with toluene (100 mL). The combined organic extracts were washed with H_2O (100 mL). The combined aqueous extracts were acidified with 2 M HCl to pH 1 and the precipitate was collected by filtration to afford the product **4.10** as a white crystalline solid.

General Method M: Synthesis of *tert*-Butyl *N*-alkylsulfamoylcarbamate 4.10

A solution of *tert*-butanol (2.62 mL, 28 mmol, 1.4 eq) in CH_2Cl_2 (5 mL) was added dropwise to stirred solution of chlorosulfonyl isocyanate (1.74 mL, 20 mmol, 1 eq) in CH_2Cl_2 (20 mL) at 0 °C. Stirred at 0 °C for 1 h. A solution of the primary amine (20 mmol, 1 eq) and triethylamine (3.07 mL, 22 mmol, 1.1 eq) in CH_2Cl_2 (5 mL) was added dropwise. Allowed to warm to rt and stirred for 16 h. The colourless suspension was washed with 0.2 M HCl (2 × 50 mL). The combined aqueous layers were washed with CH_2Cl_2 (25 mL). The combined organics extracts were dried (Na_2SO_4) and concentrated to a white solid.

General Method N: *N*-Boc Deprotection of 4.10 to Sulfamide 4.4

Trifluoroacetic acid (240 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a stirred suspension of *tert*-butyl *N*-alkylsulfamoylcarbamate **4.10** (80 mmol) in CH_2Cl_2 (100 mL) at 0 °C. The solution was stirred overnight and allowed to warm to rt, then the solution was concentrated *in vacuo*. The residue was taken up in EtOAc (75 mL), washed with sat. $NaHCO_3$ solution (2 × 50 mL), dried (Na_2SO_4) and concentrated to a colourless oil. Purification by column chromatography gave the product as a white crystalline solid.

General Method O: Synthesis of Sulfamyl Imines 4.1

N-Alkylsulfamide **4.4** (3.63 mmol, 1 eq) was added to a stirred solution of arylaldehyde **2.83** (4.00 mmol, 1.1 eq) and $Ti(OEt)_4$ (1.95g, 7.26 mmol, 2 eq) in THF (10 mL). The solution was stirred at reflux for 7 h. Allowed to cool then poured into stirred brine (100 mL), EtOAc (50 mL) was added and the mixture stirred vigorously. The mixture was then filtered through celite and flushed with further EtOAc, the filtrate was separated and the aqueous was washed with EtOAc (50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated to a cream solid. Purification by column chromatography or trituration gave the product as a white solid.

General Method P: Phenylmagnesium Chloride Addition to Sulfamyl Imines 4.1

A flame dried Schlenk was charged with **4.1** (0.5 mmol, 1 eq), and THF (10 mL) and cooled to 0 °C. Phenylmagnesium chloride (2.0 M in THF, 1 mL, 2.00 mmol, 4 eq) was added dropwise with stirring at 0 °C. The solution was stirred 18 h and allowed to warm to rt. The reaction mixture was then quenched with sat. NH_4Cl solution (20 mL), extracted with Et_2O (2 × 20 mL), the combined organic extracts were dried (Na_2SO_4) and concentrated to a light yellow oil and purified by column chromatography to give the pure product.

General Method Q: Lithium-halogen Exchange then Addition to Sulfamyl Imines 4.1

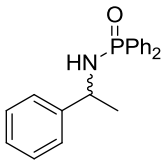
n-Butyllithium (1.6 M in hexanes, 2.5 mL, 4.0 mmol, 4 eq) was added dropwise to a stirred solution of 4-bromochlorobenzene (765.8 mg, 4.0 mmol, 4 eq) in THF (15 mL) at –78 °C and stirred for 30 min. **4.1** (1.0 mmol, 1 eq) in THF (5 mL) was added dropwise at –78 °C. The suspension was stirred for 3 h. Sat. NH_4Cl solution (20 mL) was added to quench, then extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), concentrated to a yellow oil and purified by column chromatography to give the pure product.

General Method R: Rhodium Catalysed Boronic Acid Addition Sulfamyl Imines 4.1

A flame dried Schlenk was charged with $[RhCl(C_2H_4)_2]_2$ (2.9 mg, 7.5 µmol, 1.5 mol/%), ligand (16.5 µmol, 3.3 mol/%) and toluene (0.4 mL), the orange solution was stirred at rt for 10 min. Toluene (0.6 mL), H_2O (1 mL), boronic acid **3.25** (1 mmol, 2 eq), KF (110.4 mg, 1.9 mmol, 3.8 eq) and sulfamyl imine **4.1** (0.5 mmol, 1 eq) were added sequentially. The biphasic mixture was gently stirred at 35 °C for 16 h. H_2O (10 mL) added and washed with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. Unreacted starting material could be removed by stirring residue in 1:1 CH_2Cl_2:2 M HCl (10 mL). Purification by column chromatography gave product.

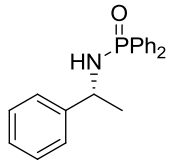
6.2 Compound Data

***P,P*-Diphenyl-*N*-(1-phenylethyl)phosphinic amide (±)-2.21a**[79]



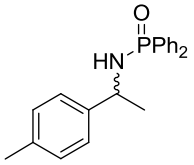
Prepared from **2.20a** (183.2 mg, 0.6 mmol) using general method **B** to give the product (177.4 mg, 92%); **R_f** 0.16 (EtOAc); **M.p.** 160-163 °C; lit. 158-162 °C;[270] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3379, 3063, 1439, 1408, 1184, 1124, 1108, 959; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.93-7.88 (m, 2H, CH_{aryl}), 7.85-7.80 (m, 2H, CH_{aryl}), 7.51-7.22 (m, 11H, CH_{aryl}), 4.44-4.35 (m, 1H, NHC*H*), 3.20 (dd, *J* = 8.8, 5.6 Hz, 1H, N*H*CH), 1.57 (d, *J* = 6.8 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 145.0 (C, d, $^3J_{CP}$ = 6.1 Hz), 133.1 (C, d, $^1J_{CP}$ = 127 Hz), 132.4 (CH, d, $^2J_{CP}$ = 9.1 Hz), 132.1 (C, d, $^1J_{CP}$ = 130 Hz), 131.8 (CH, d, $^2J_{CP}$ = 9.1 Hz), 131.75 (CH), 131.67 (CH, d, $^4J_{CP}$ = 3.0 Hz), 128.5 (CH), 128.4 (CH), 128.3 (CH, d, $^3J_{CP}$ = 12.2 Hz), 127.0 (CH), 125.9 (CH), 51.0 (CH), 25.9 (CH_3, d, $^3J_{CP}$ = 4.5 Hz); **^{31}P NMR** (161.7 MHz, $CDCl_3$) δ_P 22.5; **HRMS** (ESI Positive) calcd. for $C_{20}H_{20}NOP$, [M+Na] 344.1175, found 344.1164. These data were consistent with literature values.[271]

(*R*)-*P*,*P*-Diphenyl-*N*-(1-phenylethyl)phosphinic amide (*R*)-2.21a[79]



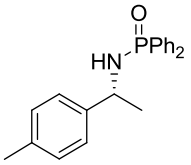
Prepared from **2.20a** (183.2 mg, 0.6 mmol) using general method **C** to give the product (121.4 mg, 63%). Analytical data as for **(±)-2.21a** except: $[\alpha]_D$ = +31.0 (*c* = 1.07, MeOH, for 93% *ee* material; lit.[270] −35.5 for 97% *ee S* antipode, *c* = 0.78, MeOH).

***P*,*P*-Diphenyl-*N*-(1-*p*-tolylethyl)phosphinic amide (±)-2.21b**[95]



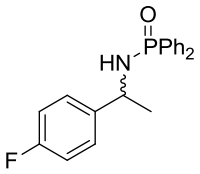
Prepared from **2.20b** (115.0 mg, 0.6 mmol) using general method **B** to give the product (166.9 mg, 83%); $\mathbf{R_f}$ 0.30 (EtOAc); **M.p.** 126-128 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3379, 3011, 2983, 1439, 1184, 1124, 1098, 960; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.94-7.81 (m, 4H, CH_{aryl}), 7.51-7.35 (m, 6H, CH_{aryl}), 7.18 (d, *J* = 7.7 Hz, 2H, CH_{aryl}), 7.12 (d, *J* = 7.7 Hz, 2H, CH_{aryl}), 4.41-4.31 (m, 1H, NHC*H*), 3.15 (dd, *J* = 9.6, 6.0 Hz, 1H, N*H*CH), 2.33 (s, 3H, $ArCH_3$), 1.56 (d, *J* = 6.8 Hz, 3H, $CHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 142.0 (C, d, $^3J_{CP}$ = 6.1 Hz), 136.6 (CH), 133.2 (C, d, $^1J_{CP}$ = 128 Hz), 132.4 (CH, d, $^2J_{CP}$ = 10.7 Hz), 132.1 (C, d, $^1J_{CP}$ = 130 Hz), 131.9 (CH, d, $^2J_{CP}$ = 10.7 Hz), 131.73 (CH, d, $^4J_{CP}$ = 3.0 Hz), 131.66 (CH, d, $^4J_{CP}$ = 3.1 Hz), 129.2 (CH), 128.4 (CH, d, $^3J_{CP}$ = 12.2 Hz), 128.3 (CH, d, $^3J_{CP}$ = 12.2 Hz), 125.8 (CH), 50.8 (CH), 25.9 (CH_3, d, $^3J_{CP}$ = 3.0 Hz), 21.0 (CH_3); **^{31}P NMR** (161.7 MHz, $CDCl_3$) δ_P 22.4; **HRMS** (ESI Positive) calcd. for $C_{21}H_{22}NOP$, [M+H] 336.1512, found 336.1509. These data were consistent with literature values.[95]

(*R*)-*P,P*-Diphenyl-*N*-(1-*p*-tolylethyl)phosphinic amide (*R*)-2.21b[95]



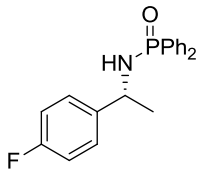
Prepared from **2.20b** (115.0 mg, 0.6 mmol) using general method **C** to give the product (118.6 mg, 59%). Analytical data as for **(±)-2.21b** except: $[\alpha]_D$ = +26.1 (*c* = 1.03, MeOH, for 92% *ee* material; lit.[95] −66.5 for 97% *ee S* antipode, *c* = 1.08, MeOH (8 °C)).

***N*-(1-(4-Fluorophenyl)ethyl)-*P,P*-diphenylphosphinic amide (±)-2.21c**[95]



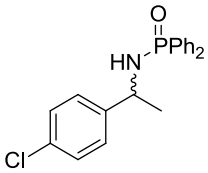
Prepared from **2.20c** (194.0 mg, 0.6 mmol) using general method **B** to give the product (189.4 mg, 93%); $\mathbf{R_f}$ 0.16 (EtOAc); **M.p.** 153-155 °C; lit. 157-159 °C;[272] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3378, 2894, 1605, 1511, 1439, 1186, 1124, 1108, 960; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.92-7.88 (m, 2H, CH_{aryl}), 7.82-7.78 (m, 2H, CH_{aryl}), 7.52-7.42 (m, 4H, CH_{aryl}), 7.39-7.34 (m, 2H, CH_{aryl}), 7.27-7.23 (m, 2H, CH_{aryl}), 7.00-6.95 (m, 2H, CH_{aryl}), 4.43 (m, 1H, NHC*H*), 3.20 (dd, *J* = 8.4, 5.2 Hz, 1H, N*H*CH), 1.55 (d, *J* = 6.4 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 161.8 (C, d, $^1J_{CF}$ = 244 Hz), 140.8 (C, dd, $^3J_{CP}$ = 6.1 Hz, $^4J_{CF}$ = 3.1 Hz), 132.8 (C, d, $^1J_{CP}$ = 134 Hz), 132.3 (CH, d, $^2J_{CP}$ = 10.7 Hz), 131.90 (CH, d, $^2J_{CP}$ = 9.1 Hz), 131.90 (CH, d, $^4J_{CP}$ = 3.1 Hz), 131.8 (CH, d, $^4J_{CP}$ = 3.0 Hz), 128.4 (CH, app. t, $^3J_{CP}$ = 12.1 Hz), 127.6 (CH, d, $^3J_{CF}$ = 9.1 Hz), 115.2 (CH, d, $^2J_{CF}$ = 21.3 Hz), 50.3 (CH), 25.9 (CH_3, d, $^3J_{CP}$ = 4.6 Hz); **^{31}P NMR** (161.7 MHz, $CDCl_3$) δ_P 22.5; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F -115.8; **HRMS** (ESI Positive) calcd. for $C_{20}H_{19}FNOP$, [M+Na] 362.1081, found 362.1070. These data were consistent with literature values.[95]

(*R*)-*N*-(1-(4-Fluorophenyl)ethyl)-*P,P*-diphenylphosphinic amide (*R*)-2.21c[95]



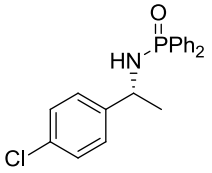
Prepared from **2.20c** (194.0 mg, 0.6 mmol) using general method **C** to give the product (99.8 mg, 49%). Analytical data as for **(±)-2.21c** except: $[\alpha]_D$ = +14.5 (*c* = 1.01, MeOH, for 84% *ee* material; lit.[95] −41.9 for 94% *ee S* antipode, *c* = 1.04, MeOH (8 °C)).

***N*-(1-(4-Chlorophenyl)ethyl)-*P,P*-diphenylphosphinic amide (±)-2.21d**[95]



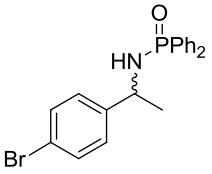
Prepared from **2.20d** (203.9 mg, 0.6 mmol) using general method **B** to give the product (204.9 mg, 96%); $\mathbf{R_f}$ 0.17 (EtOAc); **M.p.** 147-150 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3379, 2983, 1493, 1439, 1187, 1124, 1069, 959; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.92-7.87 (m, 2H, CH_{aryl}), 7.82-7.77 (m, 2H, CH_{aryl}), 7.52-7.42 (m, 4H, CH_{aryl}), 7.39-7.34 (m, 2H, CH_{aryl}), 7.28-7.25 (m, 2H, CH_{aryl}), 7.23-7.20 (m, 2H, CH_{aryl}), 4.42-4.32 (m, 1H, NHC*H*), 3.19 (dd, *J* = 9.6, 5.6 Hz, 1H, N*H*CH), 1.55 (d, *J* = 6.8 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 143.5 (C, d, $^3J_{CP}$ = 6.1 Hz), 132.8 (C, d, $^1J_{CP}$ = 127 Hz), 132.6 (C), 132.2 (CH, d, $^2J_{CP}$ = 9.1 Hz), 132.0 (C, d, $^1J_{CP}$ = 130 Hz), 131.8 (CH, d, $^2J_{CP}$ = 9.1 Hz), 131.7 (CH, d, $^4J_{CP}$ = 3.1 Hz), 128.5 (CH), 128.5 (CH, app t, $^3J_{CP}$ = 12.2 Hz), 127.4 (CH), 50.3 (CH), 25.7 (CH_3, d, $^3J_{CP}$ = 3.0 Hz); **^{31}P NMR** (161.7 MHz, $CDCl_3$) δ_P 22.6; **HRMS** (ESI Positive) calcd. for $C_{20}H_{19}ClNOP$, [M+Na] 378.0785, found 378.0793. These data were consistent with literature values.[95]

(*R*)-*N*-(1-(4-Chlorophenyl)ethyl)-*P,P*-diphenylphosphinic amide (*R*)-2.21d[95]



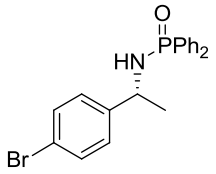
Prepared from **2.20d** (203.9 mg, 0.6 mmol) using general method **C** to give the product (133.7 mg, 60%). Analytical data as for **(±)-2.21d** except: $[\alpha]_D$ = +24.6 (*c* = 1.99, MeOH, for 86% *ee* material; lit.[95] −73.4 for 94% *ee S* antipode, *c* = 1.14, MeOH (8 °C)).

***N*-(1-(4-Bromophenyl)ethyl)-*P,P*-diphenylphosphinic amide (±)-2.21e**[273]



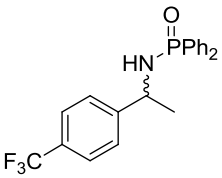
Prepared from **2.20e** (230.5 mg, 0.6 mmol) using general method **B** to give the product (208.9 mg, 87%); $\mathbf{R_f}$ 0.15 (EtOAc); **M.p.** 143-145 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3379, 2983, 1489, 1439, 1187, 1124, 1096, 959; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.92-7.87 (m, 2H, CH_{aryl}), 7.82-7.76 (m, 2H, CH_{aryl}), 7.53-7.40 (m, 6H, CH_{aryl}), 7.39-7.35 (m, 2H, CH_{aryl}), 7.16 (dt, *J* = 8.4, 2.2 Hz, 2H, CH_{aryl}), 4.40-4.30 (m, 1H, NHC*H*), 3.18 (dd, *J* = 9.6, 5.6 Hz, 1H, N*H*CH), 1.55 (d, *J* = 6.8 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 144.0 (C, d, $^3J_{CP}$ = 6.0 Hz), 132.8 (C, d, $^1J_{CP}$ = 128 Hz), 132.2 (CH, d, $^2J_{CP}$ = 9.2 Hz), 132.0 (C, d, $^1J_{CP}$ = 130 Hz), 131.8 (CH, d, $^2J_{CP}$ = 10.7 Hz), 131.7 (CH, d, $^4J_{CP}$ = 3.0 Hz), 131.4 (CH), 128.4 (CH, app t, $^3J_{CP}$ = 12.2 Hz), 127.8 (CH), 120.7 (C), 50.4 (CH), 25.7 (CH_3, d, $^3J_{CP}$ = 4.5 Hz); **^{31}P NMR** (161.7 MHz, $CDCl_3$) δ_P 22.6; **HRMS** (ESI Positive) calcd. for $C_{20}H_{19}BrNOP$, [M+Na] 422.0280, found 422.0289. These data were consistent with literature values.[273]

(*R*)-*N*-(1-(4-Bromophenyl)ethyl)-*P,P*-diphenylphosphinic amide (*R*)-2.21e[273]



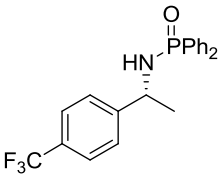
Prepared from **2.20e** (230.5 mg, 0.6 mmol) using general method **C** to give the product (156.1 mg, 65%). Analytical data as for **(±)-2.21e** except: $[\alpha]_D$ = +27.9 (*c* = 1.04, MeOH, for 75% *ee* material).

***P,P*-Diphenyl-*N*-(1-(4-(trifluoromethyl)phenyl)ethyl)phosphinic amide (±)-2.21f**[274]



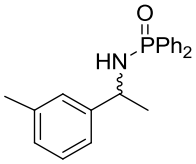
Prepared from **2.20f** (224.0 mg, 0.6 mmol) using general method **B** to give the product (207.9 mg, 89%); $\mathbf{R_f}$ 0.20 (EtOAc); **M.p.** 131-133 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3378, 2984, 1621, 1483, 1327, 1169, 1126, 1096, 960, 840; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.93-7.88 (m, 2H, CH_{aryl}), 7.81-7.75 (m, 2H, CH_{aryl}), 7.56-7.50 (m, 3H, CH_{aryl}), 7.47-7.43 (m, 3H, CH_{aryl}), 7.40-7.33 (m, 4H, CH_{aryl}), 4.50-4.40 (m, 1H, NHC*H*), 3.23 (dd, *J* = 9.2, 5.6 Hz, 1H, N*H*CH), 1.58 (d, *J* = 6.8 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 149.0 (C, d, $^3J_{CP}$ = 5.6 Hz), 132.7 (C, d, $^1J_{CP}$ = 128 Hz), 132.2 (CH, d, $^2J_{CP}$ = 9.1 Hz), 132.0 (C, d, $^1J_{CP}$ = 130 Hz), 131.9 (CH, d, $^2J_{CP}$ = 9.2 Hz), 131.8 (CH), 131.7 (CH, d, $^4J_{CP}$ = 3.0 Hz), 129.1 (C, q, $^2J_{CF}$ = 32 Hz), 128.4 (CH, d, $^3J_{CP}$ = 12.2 Hz), 128.3 (CH, d, $^3J_{CP}$ = 12.2 Hz), 126.4 (CH), 125.3 (CH, q, $^3J_{CF}$ = 3.1 Hz), 124.1 (C, q, $^1J_{CF}$ = 270 Hz), 50.6 (CH), 25.7 (CH_3, d, $^3J_{CP}$ = 3.0 Hz); **^{31}P NMR** (161.7 MHz, $CDCl_3$) δ_P 22.7; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −62.5; **HRMS** (ESI Positive) calcd. for $C_{21}H_{19}F_3NOP$, [M+Na] 412.1049, found 412.1052. These data were consistent with literature values.[274]

(*R*)-*P,P*-Diphenyl-*N*-(1-(4-(trifluoromethyl)phenyl)ethyl)phosphinic amide (*R*)-2.21f[274]



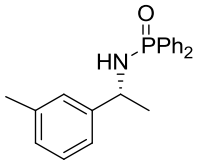
Prepared from **2.20f** (224.0 mg, 0.6 mmol) using general method **C** to give the product (163.5 mg, 70%). Analytical data as for **(±)-2.21f** except: $[\alpha]_D$ = +17.1 (*c* = 1.17, MeOH, for 78% *ee* material).

***P,P*-Diphenyl-*N*-(1-*m*-tolylethyl)phosphinic amide (±)-2.21g**[79]



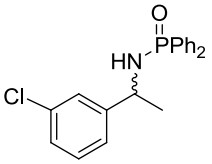
Prepared from **2.20g** (191.6 mg, 0.6 mmol) using general method **B** to give the product (197.2 mg, 98%); $\mathbf{R_f}$ 0.26 (EtOAc); **M.p.** 110-112 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3380, 2983, 1439, 1184, 1124, 965, 889; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.93-7.80 (m, 4H, CH_{aryl}), 7.51-7.35 (m, 6H, CH_{aryl}), 7.21 (t, *J* = 7.6 Hz, 1H, CH_{aryl}), 7.10-7.04 (m, 3H, CH_{aryl}), 4.41-4.31 (m, 1H, NHC*H*), 3.15 (dd, *J* = 8.8, 6.0 Hz, 1H, N*H*CH), 2.33 (s, 3H, $ArCH_3$), 1.56 (d, 3H, *J* = 6.8 Hz, $CHCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 144.9 (C, d, $^3J_{CP}$ = 6.1 Hz), 137.9 (C), 133.2 (C, d, $^1J_{CP}$ = 127 Hz), 132.8 (C), 132.3 (CH, d, $^2J_{CP}$ = 9.1 Hz), 131.7 (CH, d, $^2J_{CP}$ = 9.1 Hz), 131.6 (CH, d, $^4J_{CP}$ = 3.0 Hz), 131.5 (CH, d, $^4J_{CP}$ = 3.0 Hz), 128.2 (CH, d, $^3J_{CP}$ = 10.7 Hz), 128.1 (CH, d, $^3J_{CP}$ = 13.7 Hz), 127.6 (CH), 126.6 (CH), 122.8 (CH), 50.9 (CH), 25.8 (CH_3, d, $^3J_{CP}$ = 3.0 Hz), 21.3 (CH_3); **^{31}P NMR** (161.7 MHz, $CDCl_3$) δ_P 22.4; **HRMS** (ESI Positive) calcd. for $C_{21}H_{22}NOP$, [M+H] 336.1512, found 336.1506. These data were consistent with literature values.[270]

(*R*)-*P,P*-Diphenyl-*N*-(1-*m*-tolylethyl)phosphinic amide (*R*)-2.21g[79]



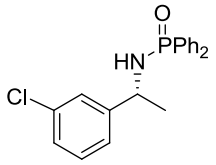
Prepared from **2.20g** (191.6 mg, 0.6 mmol) using general method **C** to give the product (120.7 mg, 60%). Analytical data as for **(±)-2.21g** except: $[\alpha]_D$ = +11.4 (*c* = 0.54, CH_2Cl_2, for 89% *ee* material; lit.[270] −38.4 for 92% *ee S* antipode, *c* = 0.57, CH_2Cl_2).

***N*-(1-(3-Chlorophenyl)ethyl)-*P,P*-diphenylphosphinic amide (±)-2.21h**



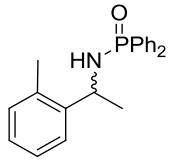
Prepared from **2.20h** (203.9 mg, 0.6 mmol) using general method **B** to give the product (200.8 mg, 94%); R_f 0.19 (EtOAc); **M.p.** 168-170 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3377, 2986, 1439, 1189, 1124, 1108, 963; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.93-7.87 (m, 2H, CH_{aryl}), 7.82-7.77 (m, 2H, CH_{aryl}), 7.53-7.42 (m, 4H, CH_{aryl}), 7.39-7.34 (m, 2H, CH_{aryl}), 7.24-7.14 (m, 4H, CH_{aryl}), 4.42-4.32 (m, 1H, NHC*H*), 3.22 (dd, 1H, *J* = 9.6, 5.6 Hz, N*H*CH), 1.55 (d, 3H, *J* = 6.8 Hz, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 147.1 (C, d, $^3J_{CP}$ = 5.9 Hz), 134.3 (C), 132.8 (C, d, $^1J_{CP}$ = 128 Hz), 132.3 (CH, d, $^2J_{CP}$ = 10.2 Hz), 131.9 (C, d, $^1J_{CP}$ = 129 Hz), 131.9 (CH, d, $^4J_{CP}$ = 2.9 Hz), 131.8 (CH, d, $^4J_{CP}$ = 4.3 Hz), 129.8 (CH), 128.5 (CH, app t, $^3J_{CP}$ = 13.1 Hz), 127.2 (CH), 126.1 (CH), 124.3 (CH), 50.6 (CH), 25.8 (CH_3, d, $^3J_{CP}$ = 2.9 Hz); **^{31}P NMR** (161.7 MHz, $CDCl_3$) δ_P 22.7; **HRMS** (ESI Positive) calcd. for $C_{20}H_{19}ClNOP$, [M+H] 356.0966, found 356.0974; Anal. Calc. for $C_{20}H_{19}ClNOP$: C, 67.51; H, 5.38; N, 3.94%. Found: C, 67.36; H, 5.36; N, 3.88%.

(*R*)-*N*-(1-(3-Chlorophenyl)ethyl)-P,P-diphenylphosphinic amide (*R*)-2.21h



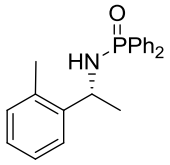
Prepared from **2.20h** (203.9 mg, 0.6 mmol) using general method **C** to give the product (94.0 mg, 44%). Analytical data as for **(±)-2.21h** except: $[\alpha]_D$ = +15.5 (*c* = 1.06, MeOH, for 78% *ee* material).

***P,P*-Diphenyl-*N*-(1-*o*-tolylethyl)phosphinic amide (±)-2.21i**



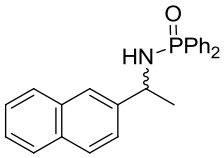
Prepared from **2.20i** (191.6 mg, 0.6 mmol) using general method **B** to give the product (187.1 mg, 93%); $\mathbf{R_f}$ 0.13 (1:1 CH_2Cl_2:EtOAc); **M.p.** 201-204 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3382, 2984, 1439, 1183, 1125, 1086, 958; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.93-7.87 (m, 2H, CH_{aryl}), 7.76-7.71 (m, 2H, CH_{aryl}), 7.51-7.40 (m, 5H, CH_{aryl}), 7.33-7.28 (m, 2H, CH_{aryl}), 7.25 (t, *J* = 6.8 Hz, 1H, CH_{aryl}), 7.14 (td, *J* = 7.4, 1.2 Hz, 1H, CH_{aryl}), 7.05 (d, *J* = 7.6 Hz, 1H, CH_{aryl}), 4.65-4.55 (m, 1H, NHC*H*), 3.28 (dd, *J* = 8.8, 5.6 Hz, 1H, N*H*CH), 2.00 (s, 3H, $ArCH_3$), 1.50 (d, *J* = 6.4 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 143.7 (C, d, $^3J_{CP}$ = 7.3 Hz), 134.0 (C), 133.2 (C, d, $^1J_{CP}$ = 125 Hz), 132.4 (CH, d, $^2J_{CP}$ = 8.7 Hz), 131.8 (CH, d, $^2J_{CP}$ = 8.7 Hz), 131.8 (CH, d, $^4J_{CP}$ = 2.9 Hz), 131.7 (CH, d, $^4J_{CP}$ = 2.9 Hz), 131.3 (C), 130.3 (CH), 128.4 (CH, d, $^3J_{CP}$ = 11.6 Hz), 128.3 (CH, d, $^3J_{CP}$ = 13.1 Hz), 126.8 (CH), 126.5 (CH), 124.7 (CH), 47.1 (CH), 26.0 (CH_3, d, $^3J_{CP}$ = 2.9 Hz), 18.8 (CH); **^{31}P NMR** (161.7 MHz, $CDCl_3$) δ_P 22.7; **HRMS** (ESI Positive) calcd. for $C_{21}H_{22}NOP$, [M+H] 336.1512, found 336.1499.

(*R*)-*P*,*P*-Diphenyl-*N*-(1-*o*-tolylethyl)phosphinic amide (*R*)-2.21i



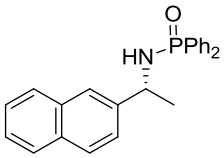
Prepared from **2.20i** (191.6 mg, 0.6 mmol) using general method **C** to give the product (68.4 mg, 34%). Analytical data as for **(±)-2.21i** except: $[\alpha]_D$ = +7.1 (*c* = 1.02, MeOH, for 79% *ee* material).

***N*-(1-(Naphthalen-2-yl)ethyl)-*P*,*P*-diphenylphosphinic amide (±)-2.21j**[95]



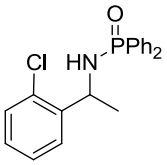
Prepared from **2.20j** (213.2 mg, 0.6 mmol) using general method **B** to give the product (205.0 mg, 92%); $\mathbf{R_f}$ 0.16 (1:1 CH_2Cl_2:EtOAc); **M.p.** 135-137 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3380, 2983, 1439, 1184, 1125; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.95-7.90 (m, 2H, CH_{aryl}), 7.86-7.77 (m, 5H, CH_{aryl}), 7.65 (br s, 1H, CH_{aryl}), 7.53- 7.40 (m, 7H, CH_{aryl}), 7.35-7.31 (m, 2H, CH_{aryl}), 4.61-4.51 (m, 1H, NHC*H*), 3.27 (dd, *J* = 8.8, 5.2 Hz, 1H, N*H*CH), 1.66 (d, *J* = 6.4 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 142.3 (C, d, $^3J_{CP}$ = 6.7 Hz), 133.2 (C), 133.1 (C, d, $^1J_{CP}$ = 127 Hz), 132.5 (C), 132.4 (CH, d, $^2J_{CP}$ = 9.6 Hz), 132.0 (C, d, $^1J_{CP}$ = 130 Hz), 131.9 (CH, d, $^2J_{CP}$ = 9.4 Hz), 131.8 (C), 131.7 (C, d, $^4J_{CP}$ = 2.4 Hz), 128.4 (CH, app t, $^3J_{CP}$ = 12.2 Hz), 127.8 (CH), 127.6 (CH), 126.1 (CH), 125.8 (CH), 124.5 (CH), 124.3 (CH), 51.1 (CH), 25.9 (CH_3, d, $^3J_{CP}$ = 3.1 Hz); **^{31}P NMR** (161.7 MHz, $CDCl_3$) δ_P 22.6; **HRMS** (ESI Positive) calcd. for $C_{24}H_{22}NOP$, [M+H] 372.1512, found 372.1503. These data were consistent with literature values.[95]

(*R*)-*N*-(1-(Naphthalen-2-yl)ethyl)-*P,P*-diphenylphosphinic amide (*R*)-2.21j[95]



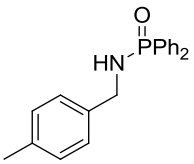
Prepared from **2.20j** (213.2 mg, 0.6 mmol) using general method **C** to give the product (162.7 mg, 73%). Analytical data as for **(±)-2.21j** except: $[\alpha]_D$ = +24.9 (*c* = 1.06, MeOH, for 84% *ee* material; lit.[95] −77.8 for 93% *ee S* antipode, *c* = 1.02, MeOH (8 °C)).

***N*-(1-(2-Chlorophenyl)ethyl)-*P,P*-diphenylphosphinic amide (±)-2.21k**



Prepared from **2.20k** (203.9 mg, 0.6 mmol) using general method **B** to give the product (194.3 mg, 73%); $\mathbf{R_f}$ 0.17 (EtOAc); **M.p.** 209-211 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3379, 2985, 1602, 1439, 1186, 1124, 1108, 958; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.91-7.86 (m, 2H, CH_{aryl}), 7.79-7.73 (m, 2H, CH_{aryl}), 7.52-7.40 (m, 4H, CH_{aryl}), 7.38-7.30 (m, 3H, CH_{aryl}), 7.28-7.23 (m, 2H, CH_{aryl}), 7.16 (td, *J* = 7.6, 2.0 Hz, 1H, CH_{aryl}), 4.79-4.69 (m, 1H, NHC*H*), 3.49 (dd, *J* = 9.6, 6.0 Hz, 1H, N*H*CH), 1.57 (d, *J* = 6.8 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 142.3 (C, d, $^3J_{CP}$ = 5.6 Hz), 132.9 (C, d, $^1J_{CP}$ = 127 Hz), 132.3 (CH, d, $^2J_{CP}$ = 9.6 Hz), 132.0 (C), 131.9 (C), 131.8 (CH, d, $^2J_{CP}$ = 9.4 Hz), 131.7 (CH), 131.2 (C d, $^1J_{CP}$ = 130 Hz), 129.8 (CH), 128.4 (CH, d, $^3J_{CP}$ = 12.4 Hz), 128.2 (CH, d, $^3J_{CP}$ = 12.5 Hz), 128.2 (CH), 127.4 (CH), 127.1 (CH), 49.1 (CH), 25.0 (CH_3, d, $^3J_{CP}$ = 3.7 Hz); **^{31}P NMR** (161.7 MHz, $CDCl_3$) δ_P 22.8; **HRMS** (ESI Positive) calcd. for $C_{20}H_{19}ClNOP$, [M+Na] 378.0785, found 378.0781.

***N*-(4-Methylbenzyl)-*P,P*-diphenylphosphinic amide 2.88b**[275]



Diphenylphosphinic chloride (0.75 mL, 3.93 mmol) was added dropwise to triethylamine (1.09 mL, 7.86 mmol) and 4-methyl benzylamine (0.5 mL, 3.93 mmol) in CH_2Cl_2 (25 mL) at 0 °C.

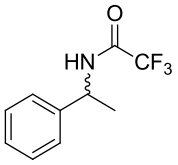
The solution was stirred at 0 °C for 1 h and rt for 45 min before washing with water (2 × 20 mL) and brine (20 mL). The organics were dried (Na_2SO_4) and concentrated to a yellow oil. Purification by column chromatography (EtOAc) gave **2.88b** as a white crystalline solid (1.04 g, 83%); **R_f** 0.22 (EtOAc); **M.p.** 110-112 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 2984, 1439, 1400, 1183, 1124; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.97-7.91 (m, 4H, CH_{aryl}), 7.52-7.42 (m, 6H, CH_{aryl}), 7.25 (d, *J* = 7.2 Hz, 2H, CH_{aryl}), 7.14 (d, *J* = 8.0 Hz, 2H, CH_{aryl}), 4.09 (t, *J* = 7.2 Hz, 2H, CH_2), 3.11 (q, *J* = 6.2 Hz, 1H, NH), 2.33 (s, 3H, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 137.1 (C), 136.5 (C, d, $^3J_{CP}$ = 7.3 Hz), 132.2 (C, d, $^1J_{CP}$ = 128 Hz), 132.1 (CH, d, $^2J_{CP}$ = 9.2 Hz), 131.8 (CH, d, $^4J_{CP}$ = 3.0 Hz), 129.3 (CH), 128.5 (CH, d, $^3J_{CP}$ = 13.7 Hz), 127.7 (CH), 44,4 (CH_2), 21.0 (CH_3); **^{31}P NMR** (161.7 MHz, $CDCl_3$) δ_P 23.5; **HRMS** (ESI Positive) calcd. for $C_{20}H_{20}NOP$, [M+H] 322.1355, found 322.1373; Anal. Calc. for $C_{20}H_{20}NOP$: C, 74.75; H, 6.27; N, 4.36%. Found: C, 74.60; H, 6.30; N, 4.33%.

Table 69

No.	Ar	X	Column	Programme	Retention times [min]
2.93a	Ph	CF_3	CP-ChiraSil-Dex CB[a]	100 °C (isothermal)	(*R*) 17.7 (*S*) 18.2
2.93b	4-MeC_6H_4	CH_3	CP-ChiraSil-Dex CB	165 °C (isothermal)	(*R*) 9.0 (*S*) 9.3
2.93c	4-FC_6H_4	CF_3	CP-ChiraSil-Dex CB	100 °C (isothermal)	(*R*) 22.6 (*S*) 23.6
2.93d	4-ClC_6H_4	CF_3	CP-ChiraSil-Dex CB	120 °C (isothermal)	(*R*) 22.0 (*S*) 22.7
2.93e	4-BrC_6H_4	CF_3	CP-ChiraSil-Dex CB	115 to 125 °C at 0.2 °C/min + 15 min at 125 °C	(*R*) 43.1 (*S*) 43.8
2.93f	4-$CF_3C_6H_4$	CF_3	CP-ChiraSil-Dex CB	100 °C (isothermal)	(*R*) 35.1 (*S*) 35.9
2.93g	3-MeC_6H_4	CF_3	2,6-γ-cyclodextrin[b]	70 °C (isothermal)	(*S*) 134.0 (*R*) 134.1
2.93h	3-ClC_6H_4	CF_3	CP-ChiraSil-Dex CB	115 °C (isothermal)	(*R*) 25.6 (*S*) 27.7
2.93i	2-MeC_6H_4	CF_3	CP-ChiraSil-Dex CB	100 °C (isothermal)	(*R*) 22.5 (*S*) 23.0
2.93j	2-Naphthyl	CH_3	CP-ChiraSil-Dex CB	160 °C (isothermal)	(*S*) 47.5 (*R*) 49.6
2.93k	2-ClC_6H_4	CF_3	CP-ChiraSil-Dex CB	120 °C (isothermal)	(*R*) 12.1 (*S*) 13.3

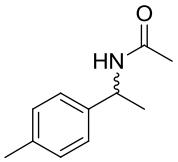
[a] Column: CP-ChiraSil-Dex CB: 0.25 mm x 0.25 μm x 25 m, [b] Column: Octakis(2,6-di-O-methyl-3-O-pentyl)-γ-cyclodextrin 0.25 μm id (60% in OV 1701 w/w).

2,2,2-Trifluoro-*N*-(1-phenylethyl)acetamide (±)-2.93a[276]



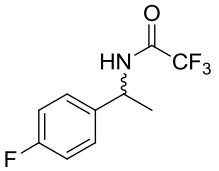
Prepared directly from **(±)-2.21a** by general method **D**; $\mathbf{R_f}$ 0.50 (CH_2Cl_2); **M.p.** 90-92 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3430, 1724, 1530, 1171; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.41-7.37 (m, 2H, CH_{aryl}), 7.35-7.31 (m, 3H, CH_{aryl}), 6.42 (br s, 1H, N*H*CH), 5.16 (quintet, *J* = 7.2 Hz, 1H, NHC*H*), 1.60 (d, *J* = 6.8 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 156.3 (C, q, $^2J_{CF}$ = 36.6 Hz), 140.9 (C), 129.0 (CH), 128.1 (CH), 126.1 (CH), 115.8 (C, q, $^1J_{CF}$ = 287 Hz), 49.8 (CH), 21.0 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −75.4; **HRMS** (ESI Negative) calcd. for $C_{10}H_{10}F_3NO$, [M−H] 216.0642, found 216.0644. These data were consistent with literature values.[276]

***N*-(1-*p*-Tolylethyl)acetamide (±)-2.93b**[277]



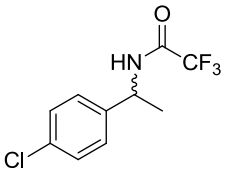
Prepared directly from **(±)-2.21a** by general method **D**; $\mathbf{R_f}$ 0.11 (1:1 pet. ether:EtOAc); **M.p.** 48-51 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3442, 3011, 1711, 1665, 1363; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.19 (d, *J* = 8.0 Hz, 2H, CH_{aryl}), 7.11 (d, *J* = 7.6 Hz, 2H, CH_{aryl}), 6.40 (br d, *J* = 7.2 Hz, 1H, N*H*CH), 5.05 (quintet, *J* = 7.2 Hz, 1H, NHC*H*), 2.31 (s, 3H, $ArCH_3$), 1.92 (s, 3H, $COCH_3$), 1.43 (d, *J* = 6.8 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.2 (C), 140.3 (C), 136.5 (C), 130.0 (CH), 126.9 (CH), 48.3 (CH), 23.0 (CH_3), 21.9 (CH_3), 20.8 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{11}H_{15}NO$, [M+H] 178.1226, found 178.1218. These data were consistent with literature values.[277]

2,2,2-Trifluoro-*N*-(1-(4-fluorophenyl)ethyl)acetamide (±)-2.93c



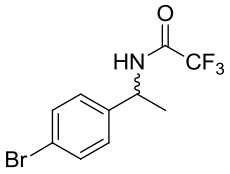
Prepared directly from **(±)-2.21c** by general method **D**; $\mathbf{R_f}$ 0.53 (CH_2Cl_2); **M.p.** 55-57 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3429, 1723, 1607, 1513, 1170, 837; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.31-7.26 (m, 2H, CH_{aryl}), 7.07-7.03 (m, 2H, CH_{aryl}), 6.48 (br s, 1H, N*H*CH), 5.12 (quintet, *J* = 7.2 Hz, 1H, NHC*H*), 1.58 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 162.4 (C, d, $^1J_{CF}$ = 245 Hz), 156.3 (C, q, $^2J_{CF}$ = 37.1 Hz), 136.7 (C, d, $^4J_{CF}$ = 3.0 Hz), 127.9 (CH, d, $^3J_{CF}$ = 7.6 Hz), 115.9 (CH, d, $^2J_{CF}$ = 21.3 Hz), 115.7 (C, d, $^1J_{CF}$ = 286 Hz), 49.1 (CH), 21.0 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −75.9, −113.8; **HRMS** (ESI Negative) calcd. for $C_{10}H_9F_4NO$, [M−H] 234.0548, found 234.0543.

***N*-(1-(4-Chlorophenyl)ethyl)-2,2,2-trifluoroacetamide (±)-2.93d**



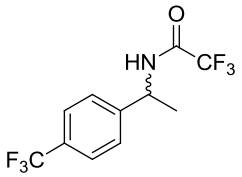
Prepared directly from **(±)-2.21d** by general method **D**; $\mathbf{R_f}$ 0.67 (CH_2Cl_2); **M.p.** 106-107 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3429, 1725, 1530, 1495, 1170, 828; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.36-7.33 (m, 2H, CH^1), 7.27-7.24 (m, 2H, CH^2), 6.47 (br s, 1H, N*H*CH), 5.11 (quintet, *J* = 7.2 Hz, 1H, NHC*H*), 1.57 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 156.4 (C, q, $^2J_{CF}$ = 36.6 Hz), 139.4 (C), 133.9 (C), 129.1 (CH), 127.5 (CH), 115.7 (C, q, $^1J_{CF}$ = 286 Hz), 49.2 (CH), 21.0 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −75.9; **HRMS** (ESI Negative) calcd. for $C_{10}H_9ClF_3NO$, [M−H] 250.0252, found 250.0242; Anal. Calc. for $C_{10}H_9ClF_3NO$: C, 47.73; H, 3.61; N, 5.57%. Found: C, 47.60; H, 3.59; N, 5.40%.

***N*-(1-(4-Bromophenyl)ethyl)-2,2,2-trifluoroacetamide (±)-2.93e**[278]



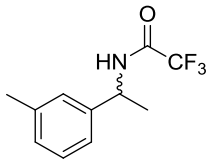
Prepared directly from **(±)-2.21e** by general method **D**; $\mathbf{R_f}$ 0.57 (CH_2Cl_2); **M.p.** 123-125 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3429, 1725, 1530, 1492, 1170, 1010, 824; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.52-7.49 (m, 2H, CH^1), 7.21-7.18 (m, 2H, CH^2), 6.47 (br s, 1H, N*H*CH), 5.10 (quintet, *J* = 7.2 Hz, 1H, NHC*H*), 1.57 (d, *J* = 7.0 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 156.3 (C, q, $^2J_{CF}$ = 36.6 Hz), 139.9 (C), 132.1 (CH), 127.8 (CH), 122.0 (C), 115.7 (C, q, $^1J_{CF}$ = 286 Hz), 49.2 (CH), 21.0 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −75.9; **HRMS** (ESI Negative) calcd. for $C_{10}H_9BrF_3NO$, [M−H] 293.9747, found 293.9745. These data were consistent with literature values.[278]

2,2,2-Trifluoro-*N*-(1-(4-(trifluoromethyl)phenyl)ethyl)acetamide (±)-2.93f



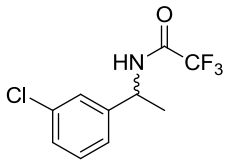
Prepared directly from **(±)-2.21f** by general method **D**; $\mathbf{R_f}$ 0.66 (CH_2Cl_2); **M.p.** 78-80 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3429, 1726, 1531, 1327, 1171, 1132, 1070, 841; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.64 (d, *J* = 8.0 Hz, 2H, CH^1), 7.44 (d, *J* = 8.4 Hz, 2H, CH^2), 6.48 (br s, 1H, N*H*CH), 5.19 (quintet, *J* = 7.2 Hz, 1H, NHC*H*), 1.61 (d, *J* = 7.2 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 156.5 (C, q, $^2J_{CF}$ = 37.1 Hz), 144.9 (C), 130.4 (C, q, $^2J_{CF}$ = 32.5 Hz), 126.5 (CH), 126.0 (CH, q, $^3J_{CF}$ = 3.7 Hz), 123.9 (C, q, $^1J_{CF}$ = 271 Hz), 115.7 (C, q, $^1J_{CF}$ = 286 Hz), 49.5 (CH), 21.2 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −62.7, −75.8; **HRMS** (ESI Negative) calcd. for $C_{11}H_9F_6NO$, [M−H] 284.0516, found 284.0515. This compound is reported in the literature but no analytical data are quoted.[279]

2,2,2-Trifluoro-*N*-(1-*m*-tolylethyl)acetamide (±)-2.93g



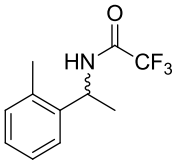
Prepared directly from **(±)-2.21g** by general method **D**; $\mathbf{R_f}$ 0.85 (CH_2Cl_2); **M.p.** 65-66 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3429, 1722, 1529, 1171; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.28-7.25 (td, *J* = 7.2, 1.2 Hz, 1H, CH_{aryl}), 7.14-7.10 (m, 3H, CH_{aryl}), 6.52 (br s, 1H, N*H*CH), 5.10 (quintet, *J* = 6.8 Hz, 1H, NHC*H*), 2.36 (s, 3H, $ArCH_3$), 1.57 (d, *J* = 6.8 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 156.2 (C, q, $^2J_{CF}$ = 36.6 Hz), 140.8 (C), 138.8 (C), 128.9 (CH), 128.9 (CH), 127.0 (CH), 123.1 (CH), 115.8 (C, q, $^1J_{CF}$ = 287 Hz), 49.9 (CH), 21.4 (CH_3), 21.1 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −75.9; **HRMS** (ESI Negative) calcd. for $C_{11}H_{12}F_3NO$, [M−H] 230.0798, found 230.0810.

***N*-(1-(3-Chlorophenyl)ethyl)-2,2,2-trifluoroacetamide (±)-2.93h**



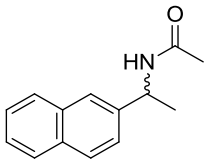
Prepared directly from **(±)-2.21h** by general method **D**; $\mathbf{R_f}$ 0.67 (CH_2Cl_2); **M.p.** 52-54 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3428, 2984, 1724, 1530, 1169, 879; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.33-7.28 (m, 3H, CH_{aryl}), 7.21-7.19 (m, 1H, CH_{aryl}), 6.59 (br s, 1H, N*H*CH), 5.10 (quintet, *J* = 7.2 Hz, 1H, NHC*H*), 1.57 (d, *J* = 7.0 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 156.5 (C, q, $^2J_{CF}$ = 37.1 Hz), 143.0 (C), 134.9 (C), 130.4 (CH), 128.4 (CH), 126.4 (CH), 124.5 (CH), 115.8 (C, q, $^1J_{CF}$ = 286 Hz), 49.4 (CH), 21.1 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −75.8; **HRMS** (ESI Negative) calcd. for $C_{10}H_9F_3ClNO$, [M−H] 250.0252, found 250.0252; Anal. Calc. for $C_{10}H_9F_3ClNO$: C, 47.73; H, 3.61; N, 5.57%. Found: C, 48.06; H, 3.65; N, 5.23%.

2,2,2-Trifluoro-*N*-(1-*o*-tolylethyl)acetamide (±)-2.93i



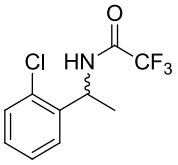
Prepared directly from **(±)-2.21i** by general method **D**; $\mathbf{R_f}$ 0.55 (CH_2Cl_2); **M.p.** 65-67 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3428, 3012, 1723, 1528, 1171; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.31-7.19 (m, 4H, CH_{aryl}), 6.37 (br s, 1H, N*H*CH), 5.34 (quintet, *J* = 7.2 Hz, 1H, NHC*H*), 2.37 (s, 3H, $ArCH_3$), 1.58 (d, *J* = 7.2 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 156.1 (C, q, $^2J_{CF}$ = 36.6 Hz), 138.8 (C), 136.0 (C), 131.0 (CH), 128.1 (CH), 126.6 (CH), 124.6 (CH), 115.8 (C, q, $^1J_{CF}$ = 286 Hz), 46.3 (CH), 20.5 (CH_3), 19.0 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −75.8; **HRMS** (ESI Negative) calcd. for $C_{11}H_{12}F_3NO$, [M−H] 230.0798, found 230.0801.

***N*-(1-(Naphthalen-2-yl)ethyl)acetamide (±)-2.93j**[280]



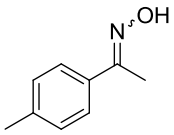
Prepared directly from **(±)-2.21j** by general method **D**; $\mathbf{R_f}$ 0.60 (1:1 pet. ether:EtOAc); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3441, 3011, 1666, 1507; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.82-7.79 (m, 3H, CH_{aryl}), 7.75 (br s, 1H, CH_{aryl}), 7.48-7.42 (m, 3H, CH_{aryl}), 5.89 (br d, *J* = 5.6 Hz, 1H, N*H*CH), 5.29 (quintet, *J* = 7.2 Hz, 1H, NHC*H*), 2.00 (s, 3H, $COCH_3$), 1.57 (d, *J* = 6.8 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.1 (C), 140.5 (C), 133.3 (C), 132.7 (C), 128.6 (CH), 127.8 (CH), 127.6 (CH), 126.2 (CH), 125.9 (CH), 124.7 (CH), 124.5 (CH), 48.8 (CH), 23.5 (CH_3), 21.6 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{14}H_{15}NO$, [M+H] 214.1226, found 214.1216. These data were consistent with literature values.[280]

***N*-(1-(2-Chlorophenyl)ethyl)-2,2,2-trifluoroacetamide (±)-2.93k**



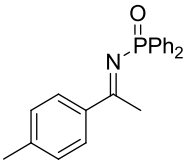
Prepared directly from **(±)-2.21k** by general method **D**; $\mathbf{R_f}$ 0.75 (CH_2Cl_2); **M.p.** 101-103 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3432, 1726, 1530, 1171, 1041; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.42-7.39 (m, 1H, CH_{aryl}), 7.34-7.31 (m, 1H, CH_{aryl}), 7.30-7.25 (m, 2H, CH_{aryl}), 6.78 (br s, 1H, N*H*CH), 5.42 (quintet, *J* = 7.2 Hz, 1H, NHC*H*), 1.61 (d, *J* = 7.2 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 156.1 (C, q, *J* = 37.1 Hz), 138.0 (C), 133.0 (C), 130.5 (CH), 129.3 (CH), 127.4 (CH), 127.4 (CH), 115.8 (C, q, *J* = 286 Hz), 48.2 (CH), 20.2 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −75.9; **HRMS** (ESI Negative) calcd. for $C_{10}H_9ClF_3NO$, [M−H] 250.0252, found 250.0255.

1-*p*-Tolylethanone oxime 2.91[281]



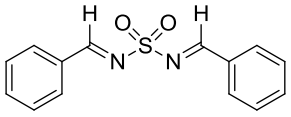
Hydroxylamine hydrochloride (903 mg, 13 mmol) and triethylamine (1.18 mL, 13 mmol) were added to stirred solution of 4-methylacetophenone (1.34 mL, 10 mmol) in EtOH (10 mL). The solution was stirred at reflux for 3 hours and then concentrated to a colourless oil, which was partitioned between water (50 mL) and EtOAc (2 × 30 mL). The organics were washed with brine (20 mL), dried ($MgSO_4$) and concentrated to a white crystalline solid (1.40 g, 93%); $\mathbf{R_f}$ 0.82 (EtOAc); **M.p.** 82-85 °C; lit. 86-88 °C;[282] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3584, 3313, 3009, 1516, 1369, 1291, 1277, 1003, 919, 823; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 9.48 (br s, 1H, OH), 7.51 (d, *J* = 8.4 Hz, 2H, CH_{aryl}), 7.18 (d, *J* = 7.6 Hz, 2H, CH_{aryl}), 2.36 (s, 3H, $ArCH_3$), 2.21 (s, 3H, N=CCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 155.9 (C), 139.3 (C), 133.6 (C), 129.2 (CH), 125.9 (CH), 21.2 (CH_3), 12.3 (CH_3); **HRMS** (ESI Positive) calcd. for $C_9H_{11}NO$, [M+H] 150.0913, found 150.0909. These data were consistent with literature values.[283]

(*E*)-*P*,*P*-Diphenyl-*N*-(1-*p*-tolylethylidene)phosphinic amide 2.92[284]



Chlorodiphenyl phosphine (0.95 mL, 5 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 20 min to a solution of **2.91** (746 mg, 5 mmol) and triethylamine (0.69 mL, 5 mmol) in CH_2Cl_2/pet. ether (15 mL) at −40 °C. The suspension was stirred at −35 °C for 90 min and then allowed to warm to rt over 2 h. The suspension was concentrated to a cream solid, dissolved in CH_2Cl_2 (25 mL), washed with sat. $NaHCO_3$ solution (20 mL) and brine (20 mL). The organics were dried ($MgSO_4$) and concentrated to a cream solid which was purified by column chromatography (1:1 pet. ether:EtOAc) to afford the product as a white solid (1.20 g, 72%); $\mathbf{R_f}$ 0.19 (1:1 pet. ether:EtOAc); **M.p.** 118-120 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3358, 2988, 1637, 1606, 1438, 1279, 1183, 833; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.00-7.95 (m, 6H, CH_{aryl}), 7.46-7.40 (m, 6H, CH_{aryl}), 7.31-7.26 (m, 2H, CH_{aryl}), 2.93 (d, J = 2.0 Hz, 3H, N=CCH_3), 2.43 (s, 3H, ArCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 181.4 (d, J = 7.6 Hz), 143.2, 136.9 (d, $^3J_{CP}$ = 23.9 Hz), 134.9 (d, $^1J_{CP}$ = 130 Hz), 131.6 (d, $^2J_{CP}$ = 9.0 Hz), 131.3 (d, $^4J_{CP}$ = 2.7 Hz), 129.2, 128.4 (d, $^3J_{CP}$ = 12.3 Hz), 128.0, 23.0 (d, $^3J_{CP}$ = 12.5 Hz), 21.5; **^{31}P NMR** (161.7 MHz, $CDCl_3$) δ_P 18.7; **HRMS** (ESI Positive) calcd. for $C_{21}H_{20}NOP$, [M+H] 334.1355, found 334.1343. These data were consistent with literature values.[284]

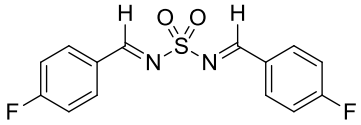
***N*,*N*'-*Bis*(phenylmethylene) sulfamide 3.85a**[207]



Prepared from benzaldehyde (5.10 mL, 50 mmol) using general method **E**. The filtrate was concentrated to a cream solid which was recrystallised from ^{i}PrOH to afford the product as white crystals (4.51 g, 66%); $\mathbf{R_f}$ 0.10 (3:1 pet. ether:EtOAc); **M.p.** 145-146 °C (^{i}PrOH); lit. 149-150 °C;[285] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 1611, 1599, 1571, 1453, 1329, 1150, 824; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 9.18 (s, 2H, N=CH), 8.01-7.98 (m, 4H, CH_{aryl}), 7.67-7.64 (m, 2H, CH_{aryl}), 7.55-7.51 (m, 4H, CH_{aryl}); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 173.2 (CH), 135.3 (CH), 132.3 (C), 131.5 (CH), 129.2 (CH); **HRMS** (ESI Positive) calcd. for $C_{14}H_{12}N_2O_2S$, [M+H]

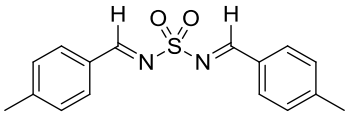
273.0692, found 273.0692; Anal. Calc. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29%. Found: C, 61.49; H, 4.50; N, 10.22%. These data were consistent with literature values.[285]

***N,N'*-*Bis*[(4-fluorophenyl)methylidene]sulfamide 3.85b**



Prepared from 4-fluorobenzaldehyde (2.15 mL, 20 mmol) using general method **E**. Large crystals formed and were collected by filtration and then physically separated from the Amberlyst® 15 to give the product as white crystals (2.28 g, 77%); $\mathbf{R_f}$ 0.70 (8:2 EtOAc:pet. ether); **M.p.** 208-210 °C; **IR** (Nujol) ν_{max}/cm^{-1} 3414, 1600, 1583, 1236, 1144, 839; **^{1}H NMR** (400.1 MHz, DMSO-d_6) δ_H 9.25 (s, 2H, N=CH), 8.23-8.18 (m, 4H, CH_{aryl}), 7.49-7.43 (m, 4H, CH_{aryl}); **^{13}C NMR** (100.6 MHz, DMSO-d_6) δ_C 172.4 (CH), 166.3 (C, d, $^1J_{CF}$ = 254 Hz), 134.4 (CH), 129.0 (C), 116.7 (CH, d, $^2J_{CF}$ = 22.9 Hz); **^{19}F NMR** (376.5 MHz, DMSO-d_6) δ_F −101.8; **HRMS** (ESI Positive) calcd. for $C_{14}H_{10}F_2N_2O_2S$, [M+Na] 331.0323, found 331.0334; Anal. Calc. for $C_{14}H_{10}F_2N_2O_2S$: C, 54.54; H, 3.27; N, 9.09%. Found: C, 54.31; H, 3.20; N, 9.01%.

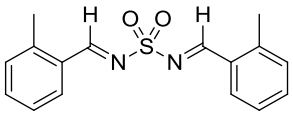
***N,N'*-*Bis*[(4-methylphenyl)methylidene]sulfamide 3.85d**[209,210]



A suspension of sulfamide (961 mg, 10 mmol), *p*-tolualdehyde (2.37 mL, 20 mmol) and methanesulfonic acid (17 µL, 0.5 mmol) in benzene (25 mL) was refluxed overnight using a Dean-Stark trap. A white precipitate formed and was collected by filtration and washed with hexanes. Trituration with ^{i}PrOH gave the product as a white powder (1.17 g, 57%); $\mathbf{R_f}$ 0.51 (1:1 pet. ether:EtOAc); **M.p.** 212-213 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3045, 1594, 1561, 1327, 1148, 829; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 9.12 (s, 2H, N=CH), 7.88 (d, J = 8.0 Hz, 4H, CH_{aryl}), 7.32 (d, J = 8.0 Hz, 4H, CH_{aryl}), 2.45 (s, 6H, $ArCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 172.2 (CH), 146.8 (C), 131.6 (CH), 130.0 (CH), 129.8 (C), 21.1 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{16}H_{16}N_2O_2S$, [M+Na] 323.0825, found 323.0811; Anal. Calc. for $C_{16}H_{16}N_2O_2S$: C, 63.98;

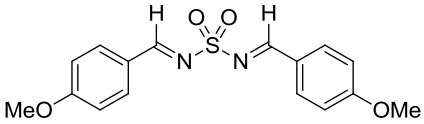
H, 5.37; N, 9.33%. Found: C, 63.81; H, 5.34; N, 9.30%. This compound is reported in the literature but no analytical data are quoted.[209,210]

***N,N'-Bis*[(2-methylphenyl)methylidene]sulfamide 3.85e**



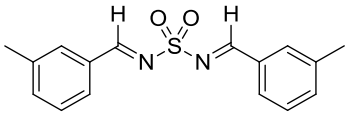
Prepared from *o*-tolualdehyde (2.31 mL, 20 mmol) using general method **E**. Hexanes was added to the filtrate and the resulting cream precipitate was filtered and recrystallised from ^{i}PrOH to afford the product as white needles (1.34g, 45%); $\mathbf{R_f}$ 0.23 (4:1 pet. ether:EtOAc); **M.p.** 139-140 °C (^{i}PrOH); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3043, 1607, 1588, 1562, 1327, 1150, 836; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 9.49 (s, 2H, N=CH), 8.09 (dd, *J* = 7.8, 1.0 Hz, 2H, CH_{aryl}), 7.51 (td, *J* = 7.6, 1.6 Hz, 2H, CH_{aryl}) 7.32 (t, *J* = 7.8 Hz, 2H, CH_{aryl}), 7.30 (dt, *J* = 7.6, 0.6 Hz, 2H, CH_{aryl}), 2.65 (s, 6H, $ArCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 171.4 (CH), 142.5 (C), 134.9 (CH), 131.6 (CH), 130.6 (CH), 130.4 (C), 126.7 (CH), 19.6 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{16}H_{16}N_2O_2S$, [M+Na] 323.0825, found 323.0823; Anal. Calc. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33%. Found: C, 63.92; H, 5.42; N, 9.23%.

***N,N'-Bis*[(4-methoxyphenyl)methylidene]sulfamide 3.85f**[285]



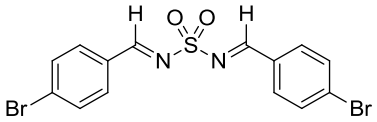
Prepared from *p*-anisaldehyde (2.25 mL, 20 mmol) using general method **E**. The filtrate was concentrated to a cream solid which was triturated with ^{i}PrOH to afford the product (2.34g, 71%); $\mathbf{R_f}$ 0.16 (3:1 pet. ether:EtOAc); **M.p.** 181-182 °C; lit. 184-185 °C;[285] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3043, 1589, 1558, 1514, 1317, 1265, 1115, 825; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 9.06 (s, 2H, N=CH), 7.94 (dt, *J* = 8.8, 2.4 Hz, 4H, CH_{aryl}), 7.00 (dt, *J* = 8.8, 2.3 Hz, 4H, CH_{aryl}), 3.90 (s, 6H, OCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 171.4 (CH), 165.4 (C), 133.9 (CH), 125.2 (C), 114.7 (CH), 55.7 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{16}H_{16}N_2O_4S$, [M+Na] 355.0723, found 355.0717; Anal. Calc. for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43%. Found: C, 57.69; H, 4.83; N, 8.48%. These data were consistent with literature values.[285]

***N,N'-Bis*[(3-methylphenyl)methylidene]sulfamide 3.85h**



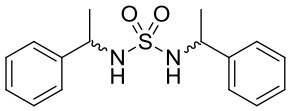
Prepared from *m*-tolualdehyde (2.36 mL, 20 mmol) using general method **E**. The filtrate was concentrated to a light brown solid which was recrystallised from ^{i}PrOH to afford the product as white crystals (2.15 g, 72%); $\mathbf{R_f}$ 0.51 (1:1 pet. ether:EtOAc); **M.p.** 101-103 °C (^{i}PrOH); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 1595, 1575, 1299, 1150, 837; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 9.14 (s, 2H, N=CH), 7.84-7.83 (m, 2H, CH_{aryl}), 7.77 (dm, *J* = 7.6 Hz, 2H, CH_{aryl}) 7.47 (dm, *J* = 7.6 Hz, 2H, CH_{aryl}), 7.41 (t, *J* = 7.6 Hz, 2H, CH_{aryl}), 2.42 (s, 6H, $ArCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 173.3 (CH), 139.2 (C), 136.2 (CH), 132.3 (C), 131.5 (CH), 129.2 (CH), 129.1 (CH), 21.1 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{16}H_{16}N_2O_2S$, [M+H] 301.1005, found 301.1007; Anal. Calc. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33%. Found: C, 63.63; H, 5.41; N, 9.31%.

***N,N'-Bis*[(4-bromophenyl)methylidene]sulfamide 3.85i**



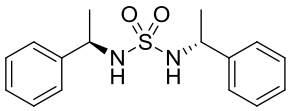
Prepared from *m*-tolualdehyde 4-bromobenzaldehyde (3.70 g, 20 mmol) using general method **E**. The resulting suspension was allowed to cool, the Amberlyst® 15 and white solid were removed by filtration. The Amberlyst® 15 was removed by hot filtration with toluene, on cooling a white solid formed which was collected by filtration (1.83 g, 43%); **M.p.** 260-262 °C; **IR** (Nujol) ν_{max}/cm^{-1} 1585, 1558, 1324, 1146, 872; **^{1}H NMR** (400.1 MHz, DMSO-d_6) δ_H 9.24 (s, 2H, N=CH), 8.03 (d, *J* = 8.4 Hz, 4H, CH_{aryl}), 7.84 (d, *J* = 8.4 Hz, 4H, CH_{aryl}); **^{13}C NMR** (100.6 MHz, DMSO-d_6) δ_C 192.4, 165.8, 132.5, 132.1, 131.3; Anal. Calc. for $C_{14}H_{10}Br_2N_2O_2S$: C, 39.09; H, 2.34; N, 6.51%. Found: C, 38.93; H, 2.28; N, 6.32%.

***N,N'*-Sulfonyl *bis*-[1-phenylethylamine] 3.96**[207]



Methylmagnesium bromide (3.0 M in Et_2O, 0.73 mL, 2.20 mmol) was added dropwise to a stirred solution of *N,N*'-*bis*(phenylmethylene) sulfamide **3.85a** (150 mg, 0.55 mmol) in Et_2O (5 mL) at 0 °C. The solution was stirred for 3 h and allowed to warm to rt, sat. NH_4Cl solution (10 mL) was added. The solution was extracted with Et_2O (2 × 20 mL), the organics dried (Na_2SO_4) and concentrated to a colourless oil which was crystallised from Et_2O/hexane to give white crystals (118 mg, 70%); $\mathbf{R_f}$ 0.82 (EtOAc); **M.p.** 77-79 °C (Et_2O/hexane); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3383, 3011, 2978, 1455, 1418, 1329, 1155, 970; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.33-7.30 (m, 2H, CH_{aryl}), 7.27-7.20 (m, 6H, CH_{aryl}), 7.14-7.11 (m, 2H, CH_{aryl}), 4.59 (d, *J* = 6.0 Hz, 1H, NHCH_{meso}), 4.53 (d, *J* = 6.4 Hz, 1H, NHCH_{rac}), 4.39 (m, 2H, N$H_{rac+meso}$CH), 1.44 (d, *J* = 6.8 Hz, 3H, CHCH_{3rac}), 1.24 (d, *J* = 6.8 Hz, 3H, CHCH_{3meso}); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 143.0 (C_{meso}), 142.6 (C_{rac}), 128.7 (CH), 127.6 (CH), 126.2 (CH_{meso}), 126.1 (CH_{rac}), 53.8 (CH_{rac}), 53.6 (CH_{meso}), 23.6 (CH_{3rac}), 23.5 (CH_{3meso}); **HRMS** (ESI Positive) calcd. for $C_{16}H_{20}N_2O_2S$, [M+H] 305.1318, found 305.1335; Anal. Calc. for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20%. Found: C, 63.09; H, 6.61; N, 9.13%. This compound is reported in the literature but no analytical data are quoted,[207] but **(*R,R*)-3.96** has data in lit.[221]

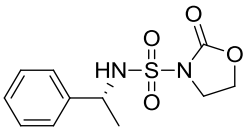
***N,N'*-Sulfonyl *bis*-[(*R*)-1-phenylethylamine] (*R,R*)-3.96**[221]



Sulfuryl chloride (0.16 mL, 2 mmol) was added dropwise to a stirred solution of (*R*)-1-phenylethylamine **(*R*)-2.1** (0.54 mL, 4.2 mmol) and triethylamine (1.67 mL, 12 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The yellow solution was allowed to warm to rt and stirred overnight. The solution was washed with 10% $NaHSO_4$ solution (2 × 50 mL), sat. $NaHCO_3$ solution (50 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated to a yellow oil. Column chromatography (3:1 hexanes:EtOAc) resulted in a cream solid (140 mg, 23%); $\mathbf{R_f}$ 0.26 (4:1 hexanes:EtOAc); **M.p.** 95-97 °C; lit. 96-97 °C;[221] $\mathbf{[\alpha]_D}$ = +15.3 (*c* = 0.64, $CHCl_3$); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3383, 2980, 1455, 1418, 1329, 1154, 970; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.27-

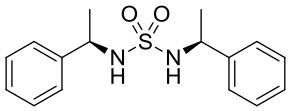
7.21 (m, 6H, CH_{aryl}), 7.15-7.13 (m, 4H, CH_{aryl}), 4.46-4.38 (m, 4H, NHC*H* and N*H*CH), 1.46 (d, *J* = 6.4 Hz, 6H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 142.5 (C), 128.7 (CH), 127.6 (CH), 126.1 (CH), 53.8 (CH), 23.6 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{16}H_{20}N_2O_2S$, [M+H] 305.1318, found 305.1335; Anal. Calc. for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20%. Found: C, 63.02; H, 6.61; N, 9.16%. These data were consistent with literature values.[221]

2-Oxo-*N*-((*R*)-1-phenylethyl)oxazolidine-3-sulfonamide (*R*)-3.98[286]



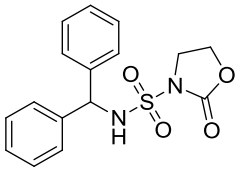
Synthesised following the procedure of Borghese *et al.*,[222] 2-bromoethanol (0.71 mL, 10 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of chlorosulfonyl isocyanate (0.87 mL, 10 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The colourless solution was stirred for 1 h at 0 °C. A solution of (*R*)-1-phenylethylamine **(*R*)-2.1** (1.42 mL, 11 mmol) and triethylamine (3.07 mL, 11 mmol) in CH_2Cl_2 (5 mL) was added dropwise to the cooled solution. The ice bath was removed and the white suspension was stirred at rt for 1 h. The reaction mixture was extracted with 0.2 M HCl (20 mL). The organics were concentrated to a white solid which was washed with water to give the product (2.66 g, 98%); **R_f** 0.20 (3:1 pet. ether:EtOAc); **M.p.** 159-162 °C; lit. 164-166 °C;[286] **$[\alpha]_D$** = +14.1 (*c* = 1.03, EtOH; lit.[286] +26.1, *c* = 1.00, EtOH); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3364, 1769, 1424, 1391, 1179, 1161, 623; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.41-7.32 (m, 5H, CH_{aryl}), 5.92 (d, *J* = 8.0 Hz, 1H, N*H*CH), 4.62 (quintet, *J* = 7.2 Hz, 1H, NHC*H*), 4.09 (dt, *J* = 6.8, 8.2 Hz, 1H, OC$H_{2\alpha}$$CH_2$N), 3.73 (dt, *J* = 6.8, 8.8 Hz, 1H, OCH_2C$H_{2\alpha}$N), 3.65 (dt, *J* = 6.4, 8.4 Hz, 1H, OC$H_{2\beta}$$CH_2$N), 3.09 (dt, *J* = 6.8, 8.8 Hz, 1H, OCH_2C$H_{2\beta}$N), 1.55 (d, *J* = 7.2 Hz, 3H, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 152.9 (C), 141.3 (C), 129.0 (CH), 128.2 (CH), 126.2 (CH), 62.4 (CH_2), 55.2 (CH), 44.6 (CH_2), 23.0 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{11}H_{14}N_2O_4S$, [M+Na] 293.0566, found 293.0557; Anal. Calc. for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 5.22; N, 10.36%. Found: C, 48.95; H, 5.19; N, 10.19%. These data were consistent with literature values.[286]

***N*-[(*R*)-1-Phenylethyl]-*N*'-[(*S*)-1-phenylethyl]sulfamide *meso*-3.96**



Following the procedure of Borghese *et al.*,[222] a suspension of (*R*)-2-oxo-*N*-(1-phenylethyl)oxazolidine-3-sulfonamide **(*R*)-3.98** (297 mg, 1.1 mmol), (*S*)-1-phenylethylamine **(*S*)-2.1** (129 µL, 1 mmol) and triethylamine (383 µL, 2.75 mmol) in MeCN (10 mL) was stirred at reflux for 3 h. The reaction mixture was concentrated and the residue was partitioned between EtOAc (30 mL) and H_2O (30 mL). The organics were washed with 1 M HCl (30 mL) and 1 M NaOH (30 mL), dried (Na_2SO_4) and concentrated to a yellow oil. This was purified by column chromatography (4:1 pet. ether:EtOAc) to give a colourless oil which formed white crystals on standing (250 mg, 82%); **R_f** 0.22 (4:1 pet. ether:EtOAc); **M.p.** 85-87 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3383, 2979, 1417, 1330, 1155, 968; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.34-7.22 (m, 10H, CH_{aryl}), 4.65 (d, *J* = 8.0 Hz, 2H, N*H*CH), 4.37 (quintet, *J* = 6.8 Hz, 2H, NHC*H*), 1.22 (d, *J* = 6.8 Hz, 6H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 143.1 (C), 128.6 (CH), 127.5 (CH), 126.2 (CH), 53.6 (CH), 23.5 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{16}H_{20}N_2O_2S$, [M+Na] 327.1138, found 327.1132; Anal. Calc. for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20%. Found: C, 63.19; H, 6.63; N, 9.16%.

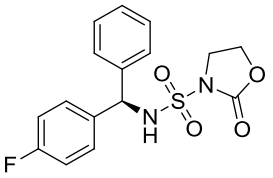
***N*-(Diphenylmethyl)-2-oxo-1,3-oxazolidine-3-sulfonamide 3.119a**



Synthesised as **(*R*)-3.98** following the procedure of Borghese *et al.*,[222] using aminodiphenylmethane **3.40a** (379 µL, 2.2 mmol). Work up gave a yellow oil which was purified using column chromatography (2:1 pet. ether:EtOAc) to give the product as a white solid (261 mg, 39%); **R_f** 0.24 (2:1 pet. ether:EtOAc); **M.p.** 175-177 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3368, 3068, 1774, 1424, 1390, 1178, 1161, 1048; **^{1}H NMR** (400.1 MHz, DMSO-d_6) δ_H 9.63 (d, *J* = 9.6 Hz, 1H, N*H*CH), 7.41-7.39 (m, 4H, CH_{aryl}), 7.35-7.32 (m, 4H, CH_{aryl}), 7.26 (tt, *J* = 7.2, 1.7 Hz, 2H, CH_{aryl}), 5.70 (d, *J* = 9.6 Hz, 1H, NHC*H*), 3.96-3.92 (m, 2H, NCH_2CH_2O), 3.76-3.72 (m, 2H, NCH_2CH_2O); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 151.7 (C), 141.1 (C), 128.4

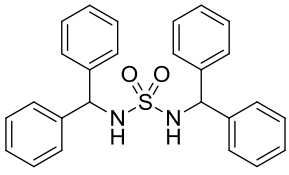
(CH), 127.3 (CH), 127.1 (CH), 62.0 (CH_2), 60.8 (CH), 45.1 (CH_2); **HRMS** (ESI Positive) calcd. for $C_{16}H_{16}N_2O_4S$, [M+Na] 355.0723, found 355.0730; Anal. Calc. for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43%. Found: C, 57.79; H, 4.82; N, 8.39%.

***N*-[(*R*)-(4-Fluorophenyl)(phenyl)methyl]-2-oxo-1,3-oxazolidine-3-sulfonamide (*R*)-3.119b**



Synthesised as **(*R*)-3.98** following the procedure of Borghese *et al.*[222] using (*R*)-(4-fluorophenyl)(phenyl)methanamine **(*R*)-3.40b** (90% *ee*, 138 mg, 0.686 mmol). Work up gave a white solid which was purified using column chromatography (2:1 pet. ether:EtOAc) to give the product as a white solid (78 mg, 36%); $\mathbf{R_f}$ 0.28 (2:1 pet. ether:EtOAc); **M.p.** 181-183 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3368, 3204, 1773, 1510, 1390, 1177, 1161, 1050; $\mathbf{[\alpha]_D}$ = +2.3 (*c* = 0.80, EtOH); **^{1}H NMR** (400.1 MHz, DMSO-d_6) δ_H 9.64 (d, *J* = 10.0 Hz, 1H, N*H*CH), 7.45-7.32 (m, 6H, CH_{aryl}), 7.29-7.25 (m, 1H, CH_{aryl}) 7.19-7.14 (m, 2H, CH_{aryl}), 5.73 (d, *J* = 9.6 Hz, 1H, NHC*H*), 4.05-3.96 (m, 2H, NCH_2CH_2O), 3.83-3.73 (m, 2H, NCH_2CH_2O); **^{13}C NMR** (100.6 MHz, DMSO-d_6) δ_C 161.3 (C, d, $^1J_{CF}$ = 241 Hz), 151.7 (C), 141.0 (C), 137.4 (C), 129.2 (CH, d, $^3J_{CF}$ = 7.6 Hz), 128.5 (CH), 127.4 (CH), 127.0 (CH), 115.2 (CH, d, $^2J_{CF}$ = 21.3 Hz), 62.1 (CH_2), 60.0 (CH), 45.1 (CH_2); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −115.2; **HRMS** (ESI Positive) calcd. for $C_{16}H_{15}FN_2O_4S$, [M+Na] 373.0629, found 373.0638; Anal. Calc. for $C_{16}H_{15}FN_2O_4S$: C, 54.85; H, 4.32; N, 8.00%. Found: C, 54.49; H, 4.23; N, 7.88%.

***N,N'*-Sulfonyl *bis*-[diphenylmethanamine] 3.100a**[207]



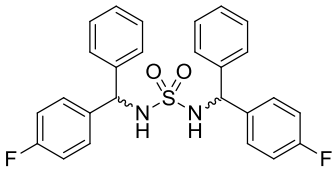
Synthesised following the borate addition procedure of Hayashi *et al.*[224] A flame dried Schlenk was charged with bromobenzene (0.13 mL, 1.25 mmol) and Et_2O (0.5 mL) then cooled to 0 °C. *n*-Butyllithium (1.6 M in hexanes, 0.78 mL, 1.25 mmol) was added dropwise. The solution was stirred at rt for 1 h, then cooled to –78 °C. Freshly distilled trimethyl borate

(0.14 mL, 1.25 mmol) was added dropwise. After stirring at –78 °C for 30 min the solution was allowed to warm to rt then imine **3.85a** (68.1 mg, 0.25 mmol), $[RhCl(C_2H_4)_2]_2$ (2.9 mg, 7.5 µmol), **(*R,R,R*)-3.99** (5.5 mg, 16.5 µmol), 3.1 M $KOH_{(aq)}$ (32.2 µL, 40 mol/%) and dioxane (2 mL) were added and the yellow suspension was stirred at 80 °C for 3 h. The mixture became brown, and was quenched with sat. Na_2CO_3 solution (20 mL), extracted with EtOAc (2 × 20 mL). The organics were dried (Na_2SO_4) and concentrated to a brown solid. Purification by column chromatography (3:1 Pet ether:EtOAc) gave the product as a yellow solid which was triturated with hexanes to give a pure white powder (80.1 mg, 75%).

Synthesised as ***meso*-3.96** following the procedure of Borghese *et al.*,[222] using aminodiphenylmethane (47 µL, 0.274 mmol). Work up gave a white solid which was purified using column chromatography (3:1 pet. ether:EtOAc) to give the product as a white solid (88.0 mg, 75%).

Prepared from **3.85a** (68.1 mg, 0.25 mmol) and **3.28a** (187 mg, 0.6 mmol) using general method **H**, purified by column chromatography (3:1 pet. ether:EtOAc) to afford the product as a white solid (83.3 mg, 78%); $\mathbf{R_f}$ 0.65 (1:1 pet. ether:EtOAc); **M.p.** 154-155 °C; **IR** (Nujol) ν_{max}/cm^{-1} 3352, 3294, 1493, 1321, 1145, 973; **^{1}H NMR** (400.1 MHz, acetone-d_6) δ_H 7.30-7.18 (m, 20H, CH_{aryl}), 6.83 (d, J = 8.0 Hz, 2H, N*H*CH), 5.59 (d, J = 8.4 Hz, 2H, NHC*H*); **^{13}C NMR** (100.6 MHz, acetone-d_6) δ_C 143.6 (C), 129.2 (CH), 128.4 (CH), 127.9 (CH), 62.1 (CH); **HRMS** (ESI Positive) calcd. for $C_{26}H_{24}N_2O_2S$, [M+H] 451.1451, found 451.1456; Anal. Calc. for $C_{26}H_{24}N_2O_2S$: C, 72.87; H, 5.64; N, 6.54%. Found: C, 72.70; H, 5.66; N, 6.54%. This compound is reported in the literature but no analytical data are quoted.[207]

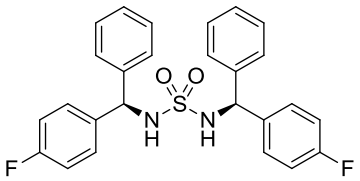
***N,N'*-Sulfonyl *bis*-[(4-fluorophenyl)(phenyl)methanamine] 3.100b**



Prepared from **3.85b** (231 mg, 0.75 mmol) using general method **G**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford the product as a white solid (217 mg, 62%) as a 1:1 mixture of *rac* and *meso* diastereoisomers; $\mathbf{R_f}$ 0.45 (3:1 pet. ether:EtOAc); **M.p.** 141-143 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3384, 1606, 1510, 1333, 1157; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H

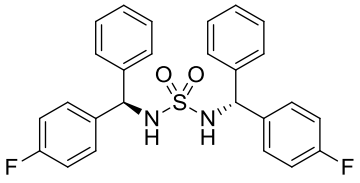
7.27-7.22 (m, 6H, CH_{aryl}), 7.12-7.06 (m, 8H, CH_{aryl}), 6.93-6.86 (m, 4H, CH_{aryl}), 5.52 (d, J = 6.8 Hz, 2H, NHC*H*), 4.94 (d, J = 6.8 Hz, 2H, N*H*CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 162.0 (C, d, $^1J_{CF}$ = 245 Hz), 140.8 ($C_{meso/rac}$), 140.7 ($C_{rac/meso}$) 136.8 (C, app. t, $^4J_{CF}$ = 3.0 Hz), 128.9 ($CH_{meso/rac}$), 128.8 ($CH_{rac/meso}$), 128.8 (CH), 127.8 (CH), 127.1 ($CH_{meso/rac}$), 127.0 ($CH_{rac/meso}$), 115.5 (CH, d, $^2J_{CF}$ = 21.4 Hz), 60.8 (CH); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F -114.66 (*rac*), -114.68 (*meso*); **HRMS** (ESI Positive) calcd. for $C_{26}H_{22}F_2N_2O_2S$, [M+Na] 487.1262, found 487.1263; Anal. Calc. for $C_{26}H_{22}F_2N_2O_2S$: C, 67.23; H, 4.77; N, 6.03%. Found: C, 67.07; H, 4.75; N, 5.95%; **HPLC**: Daicel Chiralcel OD-H and Chiralcel OD columns in series (total column length = 50 cm), 90:10 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*,*S*)-enantiomer t_R = 82.1 min, *meso* t_R = 101.0 min, (*R*,*R*)-enantiomer t_R = 106.5 min.

***N*-[(*R*)-(4-fluorophenyl)(phenyl)methyl]-*N*'-[(*S*)-(4-fluorophenyl)(phenyl)methyl]sulfamide *meso*-3.100b**



Synthesised as ***meso*-3.96** following the procedure of Borghese *et al.*,[222] using (*S*)-(4-fluorophenyl)(phenyl)methanamine **(*S*)-3.40b** (86% *ee*, 50 mg, 0.143 mmol). Work up gave a colourless oil which was purified using column chromatography (4:1 pet. ether:EtOAc) to give the product as a white solid (53.8 mg, 81%, 93:7 *dr*). Analytical data as for **3.100b** except: **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 162.1 (C, d, $^1J_{CF}$ = 245 Hz), 140.7 (C) 136.8 (C), 129.0 (CH), 128.9 (CH), 127.9 (CH), 127.1 (CH), 115.5 (CH, d, $^2J_{CF}$ = 21.3 Hz), 60.9 (CH); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F -114.64.

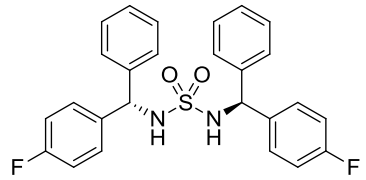
***N*,*N*'-Sulfonyl *bis*-[(*R*)-(4-fluorophenyl)(phenyl)methanamine] (*R*,*R*)-3.100b**



Prepared from **3.85b** (77.1 mg, 0.25 mmol) and **3.28a** (187 mg, 0.6 mmol) using general method **H**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford the product

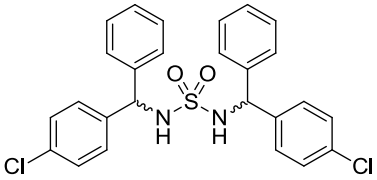
(89.7 mg, 73%, 97:3 *dr*, >99% *ee*). Analytical data as for **3.100b** except: $[\alpha]_D$ = –3.1 (*c* = 1.11, $CHCl_3$, for 97:3 dr, >99% *ee* material); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 162.1 (d, $^1J_{CF}$ = 246 Hz, C), 140.7 (C) 136.8 (C), 128.9 (CH), 128.8 (CH), 127.9 (CH), 127.1 (CH), 115.5 (d, $^2J_{CF}$ = 21.9 Hz, CH), 60.8 (CH); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F -114.61.

***N,N'*-Sulfonyl *bis*-[(*S*)-(4-fluorophenyl)(phenyl)methanamine] (*S,S*)-3.100b**



Prepared from **3.85a** (68.1 mg, 0.25 mmol) and **3.28b** (219 mg, 0.6 mmol) using general method **H**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford the product (80.5 mg, 69 %, 92:8 *dr*, >99% *ee*). Analytical data as for **(*R,R*)-3.100b** except; $[\alpha]_D$ = –0.8 (*c* = 1.00, $CHCl_3$, for 92:8 dr, >99% *ee* material).

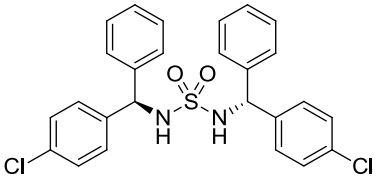
***N,N'*-Sulfonyl *bis*-[(4-chlorophenyl)(phenyl)methanamine] 3.100c**



Sulfuryl chloride (57 µL, 0.70 mmol) was added to a stirred solution of (4-chlorophenyl)(phenyl)methanamine **3.40c** (320 mg, 1.46 mmol) and triethylamine (582 µL, 4.19 mmol) in CH_2Cl_2 (10 mL) at 0 °C. Stirred overnight and allowed to warm to rt. Then washed with 10% $NaHSO_4$ solution (2 × 25 mL), sat. $NaHCO_3$ solution (25 mL) and brine (25 mL). The organics were dried (Na_2SO_4) and concentrated to a yellow oil which was purified by column chromatography (3:1 pet. ether:EtOAc) to afford the product as a white solid (61 mg, 18%) as a 1:1 mixture of *rac* and *meso* diastereoisomers; **R_f** 0.45 (3:1 pet. ether:EtOAc); **M.p.** 103-105 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3380, 1492, 1421, 1334, 1155; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.27-7.22 (m, 6H, CH_{aryl}), 7.21-7.16 (m, 4H, CH_{aryl}), 7.10-7.04 (m, 8H, CH_{aryl}), 5.50 (d, *J* = 6.8 Hz, 2H, NHC*H*), 4.90 (d, *J* = 6.8 Hz, 2H, N*H*CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 140.5 (C), 139.4 (C), 133.6 (C_{rac}), 133.5 (C_{meso}), 128.9 (CH), 128.8 (CH), 128.5 (CH_{rac}), 128.4 (CH_{meso}), 128.0 (CH), 127.1 (CH_{rac}), 127.0 (CH_{meso}), 60.9 (CH); **HRMS** (ESI Positive)

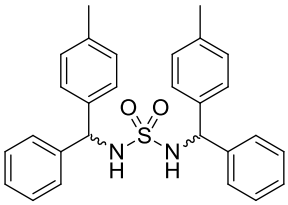
calcd. for $C_{26}H_{22}Cl_2N_2O_2S$, [M+Na] 519.0671, found 519.0681; Anal. Calc. for $C_{26}H_{22}Cl_2N_2O_2S$: C, 62.78; H, 4.46; N, 5.63%. Found: C, 62.65; H, 4.44; N, 5.55%; **HPLC**: Daicel Chiralcel OD-H and Chiralcel OD columns in series (total column length = 50 cm), 90:10 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*,*S*)-enantiomer t_R = 83.7 min, *meso* t_R = 109.2 min, (*R*,*R*)-enantiomer t_R = 117.5 min.

***N*,*N*'-Sulfonyl *bis*-[(*R*)-(4-chlorophenyl)(phenyl)methanamine] (*R*,*R*)-3.100c**



Prepared from **3.85a** (68.1 mg, 0.25 mmol) and **3.28c** (249 mg, 0.6 mmol) using general method **H**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford the product (75.5 mg, 61%, 94:6 *dr*, >99% *ee*). Analytical data as for **3.100c** except; $\mathbf{[\alpha]_D}$ = +2.7 (*c* = 1.04, $CHCl_3$, for 94:6 *dr*, >99% *ee* material); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 140.4 (C), 139.4 (C), 133.6 (C), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.0 (CH), 127.1 (CH), 60.9 (CH).

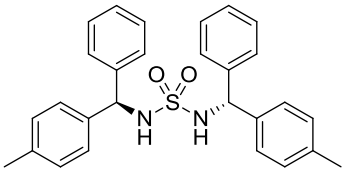
***N*,*N*'-Sulfonyl *bis*-[(4-methylphenyl)(phenyl)methylamine] 3.100d**



Prepared from **3.85a** (204 mg, 0.75 mmol) using general method **G** and *p*-tolylmagnesium bromide (1.0 M in THF, 3.0 mL, 3.0 mmol), purified by column chromatography (3:1 pet. ether:EtOAc) to afford the product as a white solid (261 mg, 76%) as a 1:1 mixture of *rac* and *meso* diastereoisomers; $\mathbf{R_f}$ 0.39 (3:1 pet. ether:EtOAc); **M.p.** 138-140 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3385, 3009, 1422, 1332, 1154, 1050, 958; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.25-7.20 (m, 6H, CH_{aryl}), 7.17-7.14 (m, 4H, CH_{aryl}), 7.03 (s, 8H, CH_{aryl}), 5.52 (d, *J* = 6.4 Hz, 2H, NHC*H*), 4.73 (d, *J* = 6.0 Hz, 2H, N*H*CH), 2.29 (s, 6H, $ArCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 141.23 ($C_{rac/meso}$), 141.21 ($C_{meso/rac}$), 138.1 (C), 137.4 (C), 129.3 (CH), 128.6 (CH), 127.6 (CH_{rac}), 127.5 (CH_{meso}), 127.13 (CH), 127.12 (CH), 61.4 (CH), 21.0 (CH_3); **HRMS** (ESI

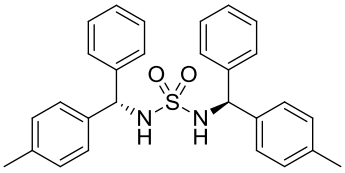
Positive) calcd. For $C_{28}H_{28}N_2O_2S$, [M+Na] 479.1764, found 479.1761; Anal. Calc. for $C_{28}H_{28}N_2O_2S$: C, 75.65; H, 6.18; N, 6.14%. Found: C, 73.60; H, 6.18; N, 6.12%; **HPLC**: Daicel Chiralcel OD-H column, 90:10 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*,*S*)-enantiomer t_R = 33.7 min, *meso* t_R = 40.8 min, (*R*,*R*)-enantiomer t_R = 47.9 min.

_N,N'_-Sulfonyl *bis*-[(*R*)-(4-methylphenyl)(phenyl)methylamine] (*R*,*R*)-3.100d



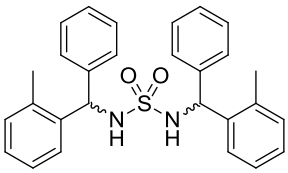
Prepared from **3.85a** (68.1 mg, 0.25 mmol) and **3.28d** (212 mg, 0.6 mmol) using general method **H**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford the product (65.8 mg, 58%, 93:7 *dr*, >99% *ee*). Analytical data as for **3.100d** except; $[\alpha]_D$ = + 3.8 (*c* = 1.01, $CHCl_3$, for 93:7 *dr*, >99% *ee* material); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 141.2 (C), 138.1 (C), 137.4 (C), 129.4 (CH), 128.6 (CH), 127.7 (CH), 127.14 (CH), 127.13 (CH), 61.4 (CH), 21.0 (CH_3).

_N,N'_-Sulfonyl *bis*-[(*S*)-(4-methylphenyl)(phenyl)methylamine] (*S*,*S*)-3.100d



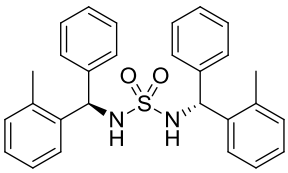
Prepared from **3.85d** (75.1 mg, 0.25 mmol) and **3.28a** (187 mg, 0.6 mmol) using general method **H**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford the product (83.6 mg, 73%, 92:8 *dr*, >99% *ee*). Analytical data as for **(*R*,*R*)-3.100d** except; $[\alpha]_D$ = –5.2 (*c* = 1.27, $CHCl_3$, for 92:8 *dr*, >99% *ee* material).

***N,N'*-Sulfonyl *bis*-[(2-methylphenyl)(phenyl)methylamine] 3.100e**



Prepared from **3.85e** (225 mg, 0.75 mmol) using general method **G**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford the product as a white solid (235 mg, 69%) recrystallised from CH_2Cl_2/hexanes as a 1:3.4 mixture of *rac* and *meso* diastereoisomers; $\mathbf{R_f}$ 0.40 (3:1 pet. ether:EtOAc); **M.p.** 145-147 °C (CH_2Cl_2/hexanes); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3385, 3066, 3009, 1494, 1336, 1154, 1045, 960; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H *Meso* diastereoisomer: 7.28-7.04 (m, 18H, CH_{aryl}), 5.78 (d, *J* = 6.4 Hz, 2H, NHC*H*), 4.64 (d, *J* = 6.4 Hz, 2H, N*H*CH), 2.16 (s, 6H, $ArCH_3$); *Rac* diastereoisomer: 7.28-7.04 (m, 18H, CH_{aryl}), 5.81 (d, *J* = 6.4 Hz, 2H, NHC*H*), 4.62 (d, *J* = 5.6 Hz, 2H, N*H*CH), 2.18 (s, 6H, $ArCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 140.3 (C), 138.9 (C), 135.5 (C), 130.9 (CH), 128.7 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 126.5 (CH), 126.3 (CH), 58.2 (CH), 19.4 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{28}H_{28}N_2O_2S$, [M+Na] 449.1764, found 479.1772; Anal. Calc. for $C_{28}H_{28}N_2O_2S$: C, 73.65; H, 6.18; N, 6.14%. Found: C, 73.26; H, 6.18; N, 6.18%; **HPLC**: Daicel Chiralpak AD-H and Chiralpak AD columns in series (total column length = 50 cm), 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*,*S*)-enantiomer t_R = 59.8 min, *meso* t_R = 62.6 min, (*R*,*R*)-enantiomer t_R = 74.3 min.

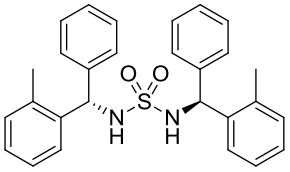
***N,N'*-Sulfonyl *bis*-[(*R*)-(2-methylphenyl)(phenyl)methylamine] (*R*,*R*)-3.100e**



Prepared from **3.85a** (68.1 mg, 0.25 mmol) and **3.28e** (212 mg, 0.6 mmol) using general method **H**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford the product (80.9 mg, 71%, >99:1 *dr*, 90% *ee*). Analytical data as for **3.100e** except; $\mathbf{[\alpha]_D}$ = –14.4 (*c* = 1.05, $CHCl_3$, for >99:1 *dr*, 90% *ee* material); **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.25-7.08 (m, 18H,

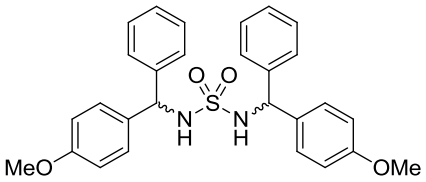
CH_{aryl}), 5.81 (d, *J* = 6.8 Hz, 2H, NHC*H*), 4.68 (d, *J* = 6.8 Hz, 2H, N*H*CH), 2.18 (s, 6H, $ArCH_3$).

_N,N'_-Sulfonyl *bis*-[(*S*)-(2-methylphenyl)(phenyl)methylamine] (*S,S*)-3.100e



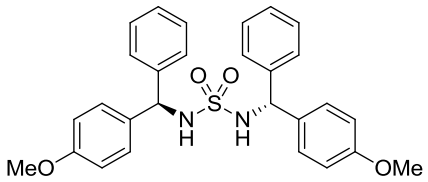
Prepared from **3.85e** (75.1 mg, 0.25 mmol) and **3.28a** (187 mg, 0.6 mmol) using general method **H**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford the product (78.5 mg, 69%, 96:4 *dr*, 98% *ee*). Analytical data as for **(*R,R*)-3.100e** except; $[\alpha]_D$ = +14.1 (*c* = 0.99, $CHCl_3$, for 96:4 *dr*, 98% *ee* material).

_N,N'_-Sulfonyl *bis*-[(4-methoxyphenyl)(phenyl)methanamine] 3.100f



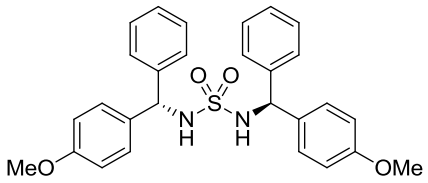
Prepared from **3.85f** (249 mg, 0.75 mmol) using general method **G** purified by column chromatography (4:1 pet. ether:EtOAc then 3:1 pet. ether:EtOAc) to give the product as a yellow oil (240 mg, 65%) as a 1:1 mixture of *rac* and *meso* diastereoisomers; $\mathbf{R_f}$ 0.11 (3:1 pet. ether:EtOAc); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3384, 3011, 1611, 1512, 1254, 1154; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.27-7.20 (m, 6H, CH_{aryl}), 7.16-7.14 (m, 4H, CH_{aryl}), 7.07-7.05 (m, 2H, CH_{aryl}), 7.04-7.03 (m, 2H, CH_{aryl}), 6.74 (m, 4H, CH_{aryl}), 5.38 (d, *J* = 6.4 Hz, 2H, NHC*H*), 4.79 (d, *J* = 6.4 Hz, 2H, N*H*CH), 3.75 (s, 3H, OCH_{3rac}), 3.74 (s, 3H, OCH_{3meso}); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 158.9 (C), 141.33 (C_{meso}), 141.30 (C_{rac}), 133.24 (C_{meso}), 133.21 (C_{rac}), 128.6 (CH), 128.5 (CH), 127.5 (CH), 127.1 (CH), 114.0 (CH), 61.0 (CH), 55.2 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{28}H_{28}N_2O_4S$, [M+Na] 511.1662, found 511.1671; **HPLC**: Daicel Chiralcel OD-H column, 80:20 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S,S*)-enantiomer t_R = 20.2 min, *meso* t_R = 30.0 min, (*R,R*)-enantiomer t_R = 41.8 min.

***N,N'*-Sulfonyl *bis*-[(*R*)-(4-methoxyphenyl)(phenyl)methanamine] (*R,R*)-3.100f**



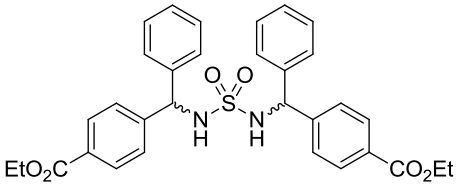
Prepared from **3.85a** (68.1 mg, 0.25 mmol) and **3.28f** (241 mg, 0.6 mmol) using general method **H**, purified by column chromatography (3:1 pet. ether:EtOAc) to afford the product (88.3 mg, 72%, 92:8 *dr*, >99% *ee*). Analytical data as for **3.100f** except; $[\alpha]_D$ = +6.1 (*c* = 1.18, $CHCl_3$, for 92:8 *dr*, >99% *ee* material); **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.26-7.22 (m, 6H, CH_{aryl}), 7.18-7.16 (m, 4H, CH_{aryl}), 7.07-7.05 (m, 4H, CH_{aryl}), 6.77 (dt, *J* = 8.8, 2.5 Hz, 4H, CH_{aryl}), 5.52 (d, *J* = 6.4 Hz, 2H, NHC*H*), 4.76 (d, *J* = 6.4 Hz, 2H, N*H*CH), 3.75 (s, 6H, OCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 159.0 (C), 141.3 (C), 133.2 (C), 128.6 (CH), 128.4 (CH), 127.5 (CH), 127.1 (CH), 114.0 (CH), 61.0 (CH), 55.2 (CH_3).

***N,N'*-Sulfonyl *bis*-[(*S*)-(4-methoxyphenyl)(phenyl)methanamine] (*S,S*)-3.100f**



Prepared from **3.85f** (83.1 mg, 0.25 mmol) and **3.28a** (187 mg, 0.6 mmol) using general method **H**, purified by column chromatography (3:1 pet. ether:EtOAc) to afford the product (79.9 mg, 69%, 95:5 *dr*, >99% *ee*). Analytical data as for **(*R,R*)-3.100f** except; $[\alpha]_D$ = –7.9 (*c* = 1.01, $CHCl_3$, for >99% *ee*, 95:5 *dr* material).

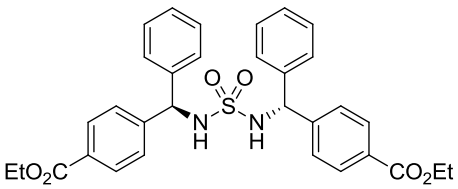
***N,N'*-Sulfonyl *bis*-[(4-(ethoxycarbonyl)phenyl)(phenyl)methanamine] 3.100g**



A flame-dried flask was charged with ethyl 4-iodobenzoate (3.32 mL, 20 mmol) and THF (25 mL) and cooled to –40 °C. *i*-Propylmagnesium bromide (2.0 M in THF, 10 mL, 20 mmol) was added dropwise, stirred at –40 °C for 2.5 h, the solution became dark brown. A second flame

dried Schlenk was charged with **3.85a** (204 mg, 0.75 mmol) and THF (10 mL) and cooled to –40 °C. The prepared aryl Grignard reagent solution (0.57 M in THF, 5.25 mL, 3.0 mmol) was added dropwise. The solution was allowed to warm to rt and stirred overnight. Then quenched with sat. NH_4Cl solution (20 mL), extracted with Et_2O (2 ×20 mL). The organics were dried (Na_2SO_4) and concentrated to a light yellow oil, purified by column chromatography (4:1 pet. ether:EtOAc) to afford the product as a white solid (449 mg, 43%) as a 1:1 mixture of *rac* and *meso* diastereoisomers; $\mathbf{R_f}$ 0.07 (4:1 pet. ether:EtOAc); **M.p.** 152-154 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3382, 2985, 1714, 1281, 1109; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.88 (dt, *J* = 8.4, 1.8 Hz, 4H, CH_{aryl}), 7.23-7.20 (m, 10H, CH_{aryl}), 7.09-7.07 (m, 4H, CH_{aryl}), 5.57 (d, *J* = 6.8 Hz, 2H, NHC*H*), 5.11 (d, *J* = 7.2 Hz, 2H, N*H*CH), 4.35 (q, *J* = 7.1 Hz, 2H, OCH_{2meso}) overlapped by 4.34 (q, *J* = 7.2 Hz, 2H, OCH_{2rac}), 1.372 (t, *J* = 7.0 Hz, 3H, CH_2CH_{3meso}) overlapped by 1.367 (t, *J* = 7.2 Hz, 3H, CH_2CH_{3rac}); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 166.1 (C), 145.7 (C), 140.3 (C), 129.9 (CH), 129.8 (C), 128.9 (CH), 128.0 (CH), 127.2 (CH_{rac}), 127.1 (CH_{meso}), 127.1 (CH_{meso}), 127.0 (CH_{rac}), 61.2 (CH), 61.0 (CH_2), 14.3 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{32}H_{32}N_2O_6S$, [M+Na] 595.1873, found 595.1862; Anal. Calc. for $C_{32}H_{32}N_2O_6S$: C, 67.11; H, 5.63; N, 4.89%. Found: C, 66.76; H, 5.63; N, 4.67%; **HPLC**: Daicel Chiralcel OD-H column in series, 80:20 hexanes:^{i}PrOH; 0.5 mL/min; 200 nm; (*R*,*R*)-enantiomer t_R = 33.2 min, *meso* and (*S*,*S*)-enantiomer t_R = 44.5 min

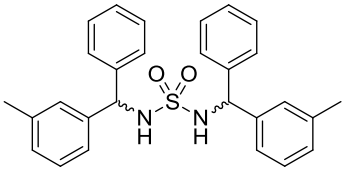
***N*,*N*'-Sulfonyl *bis*-[(*R*)-(4-(ethoxycarbonyl)phenyl)(phenyl)methanamine] (*R*,*R*)-3.100g**



Prepared from **3.85a** (68.1 mg, 0.25 mmol) and **3.28g** (317 mg, 0.6 mmol) using general method **H**, purified by column chromatography (2:1 pet. ether:EtOAc) to afford the product (52.3 mg, 37%, 97:3 *dr* and 94 % *ee* (calculated from *ee* of derived acetate **3.128g**)); Analytical data as for **3.100g** except; $\mathbf{[\alpha]_D}$ = +1.3 (*c* = 0.96, $CHCl_3$, for 94 % *ee* and 97:3 *dr* material); **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.87 (dm, *J* = 8.8 Hz, 4H, CH_{aryl}), 7.23-7.20 (m, 10H, CH_{aryl}), 7.08-7.06 (m, 4H, CH_{aryl}), 5.57 (d, *J* = 6.8 Hz, 2H, NHC*H*), 5.24 (d, *J* = 7.2 Hz, 2H, N*H*CH), 4.33 (q, *J* = 7.1 Hz, 4H, OCH_2), 1.36 (t, *J* = 7.0 Hz, 6H, CH_2CH_3); **^{13}C NMR** (100.6 MHz,

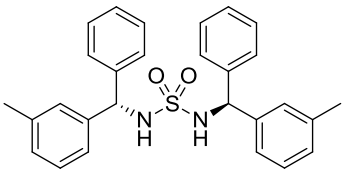
$CDCl_3$) δ_C 166.1 (C), 145.8 (C), 140.3 (C), 129.8 (CH), 129.7 (C), 128.8 (CH), 128.0 (CH), 127.2 (CH), 127.0 (CH), 61.2 (CH), 61.0 (CH_2), 14.3 (CH_3).

***N,N'*-Sulfonyl *bis*-[(3-methylphenyl)(phenyl)methylamine] 3.100h**



Prepared from **3.85h** (225 mg, 0.75 mmol) using general method **G** purified by column chromatography (4:1 pet. ether:EtOAc) to give the product as a yellow oil (231 mg, 67%) as a 1:1 mixture of *rac* and *meso* diastereoisomers; $\mathbf{R_f}$ 0.40 (4:1 pet. ether:EtOAc); **M.p.** 83-85 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3385, 3011, 1454, 1417, 1333, 1153; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.26-7.11 (m, 12H, CH_{aryl}), 7.04-7.02 (m, 2H, CH_{aryl}), 6.97-6.03 (m, 4H, CH_{aryl}), 5.53 (d, *J* = 6.4 Hz, 2H, NHC*H*), 4.77 (d, *J* = 6.4 Hz, 2H, N*H*CH), 2.26 (s, 6H, $ArCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 141.2 (C_{rac}), 141.1 (C_{meso}), 141.04 (C_{meso}), 141.01 (C_{rac}), 138.4 (C_{rac}), 138.3 (C_{meso}), 128.62 (CH_{rac}), 128.60 (CH_{meso}), 128.56 (CH), 128.5 (CH_{rac}), 128.4 (CH_{meso}), 127.9 (CH_{meso}), 127.8 (CH_{rac}), 127.6 (CH_{rac}), 127.5 (CH_{meso}), 127.2 (CH_{rac}), 127.1 (CH_{meso}), 124.2 (CH_{meso}), 124.1 (CH_{rac}), 61.5 (CH), 21.4 (CH_3); **HRMS** (ESI Positive) calcd. For $C_{28}H_{28}N_2O_2S$, [M+Na] 479.1764, found 479.1767; **HPLC**: Daicel Chiralpak AD-H and Chiralpak AD columns in series (total column length = 50 cm), 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S,S*)-enantiomer t_R = 68.8 min, *meso* t_R = 75.8 min, (*R,R*)-enantiomer t_R = 78.7 min.

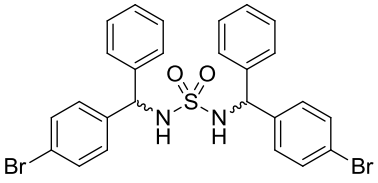
***N,N'*-Sulfonyl *bis*-[(*S*)-(3-methylphenyl)(phenyl)methylamine] (*S,S*)-3.100h**



Prepared from **3.85h** (75.1 mg, 0.25 mmol) and **3.28a** (187 mg, 0.6 mmol) using general method **H**, purified by column chromatography (3:1 pet. ether:EtOAc) to afford the product (86.1 mg, 75%, 92:8 dr, >99% *ee*). Analytical data as for **3.100h** except; $\mathbf{[\alpha]_D}$ = +1.3 (*c* = 0.94, $CHCl_3$, for 92:8 dr, >99% *ee* material); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 141.2 (C), 141.0

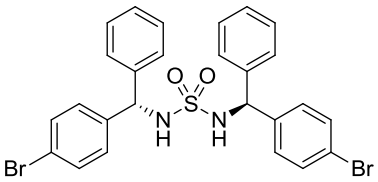
(C), 138.4 (C), 128.7 (CH), 128.56 (CH), 128.5 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 124.2 (CH), 61.6 (CH), 21.4 (CH_3).

***N,N'*-Sulfonyl *bis*-[(4-bromophenyl)(phenyl)methanamine] 3.100i**



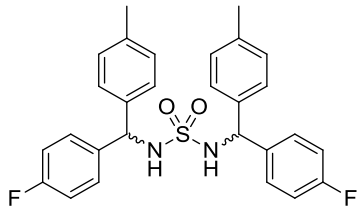
Prepared from **3.85i** (323 mg, 0.75 mmol) using general method **G** purified by column chromatography (3:1 pet. ether:EtOAc) to give the product as a yellow oil (378 mg, 86%) as a 1:1 mixture of *rac* and *meso* diastereoisomers; $\mathbf{R_f}$ 0.44 (3:1 pet. ether:EtOAc); **M.p.** 163-165 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3382, 3008, 1488, 1422, 1334, 1155, 1011; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.38-7.33 (m, 4H, CH_{aryl}), 7.28-7.24 (m, 6H, CH_{aryl}), 7.10-7.08 (m, 4H, CH_{aryl}), 7.04-7.01 (m, 4H, CH_{aryl}), 5.51 (d, *J* = 6.8 Hz, 2H, NHC*H*), 4.75 (d, *J* = 6.8 Hz, 2H, N*H*CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 140.4 (C), 139.9 (C), 131.8 (CH), 128.9 (CH), 128.8 (CH), 128.0 (CH), 127.1 (CH_{rac}), 127.0 (CH_{meso}), 121.8 (C), 61.0 (CH); **HRMS** (ESI Positive) calcd. for $C_{26}H_{22}Br_2N_2O_2S$, [M+Na] 606.9661, found 606.9646; Anal. Calc. for $C_{26}H_{22}Br_2N_2O_2S$: C, 53.26; H, 3.78; N, 4.78%. Found: C, 53.27; H, 3.77; N, 4.68%; **HPLC**: Daicel Chiralcel OD-H column, 90:10 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S,S*)-enantiomer t_R = 51.4 min, *meso* t_R = 67.6 min, (*R,R*)-enantiomer t_R = 73.5 min.

***N,N'*-Sulfonyl *bis*-[(*S*)-(4-bromophenyl)(phenyl)methanamine] (*S,S*)-3.100i**



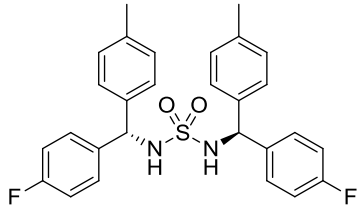
Prepared from **3.85i** (108 mg, 0.25 mmol) and **3.28a** (187 mg, 0.6 mmol) using general method **H**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford the product (87.6 mg, 62%, 91:9 dr, >99% *ee*). Analytical data as for **3.100i** except; $\mathbf{[\alpha]_D}$ = –3.3 (*c* = 1.23, $CHCl_3$, for 91:9 dr, >99% *ee* material); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 140.4 (C), 139.9 (C), 131.8 (CH), 128.9 (CH), 128.8 (CH), 128.0 (CH), 127.1 (CH), 121.7 (C), 60.9 (CH).

***N*,*N*'-Sulfonyl *bis*-[(4-fluorophenyl)(4-methylphenyl)methanamine] 3.100j**



Prepared from **3.85b** (231 mg, 0.75 mmol) using general method **G** and *p*-tolylmagnesium bromide (1.0 M in THF, 3 mL, 3.0 mmol), purified by column chromatography (3:1 pet. ether:EtOAc) to give the product as a white solid (274.4 mg, 74%) as a 1:1 mixture of *rac* and *meso* diastereoisomers; $\mathbf{R_f}$ 0.63 (3:1 pet. ether:EtOAc); **M.p.** 96-98 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3604, 3382, 3009, 1605, 1510, 1157; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.15-7.04 (m, 8H, CH_{aryl}), 7.00 (t, *J* = 7.6 Hz, 4H, CH_{aryl}), 6.95-6.88 (m, 4H, CH_{aryl}), 5.50 (d, *J* = 6.0 Hz, 2H, NHC*H*), 4.67 (d, *J* = 6.4 Hz, 2H, N*H*CH), 2.31 (s, 3H, CH_{3meso}), 2.30 (s, 3H, CH_{3rac}); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 162.0 (C, d, $^1J_{CF}$ = 245 Hz), 137.9 (C_{meso}), 137.8 (C_{rac}), 137.63 (C_{rac}), 137.60 (C_{meso}), 137.0 (C, app. t, $^4J_{CF}$ = 3.8 Hz), 129.4 (CH), 128.8 (CH, d, $^3J_{CF}$ = 7.7 Hz), 127.0 (CH_{rac}), 126.9 (CH_{meso}), 115.4 (CH, d, $^2J_{CF}$ = 21.3 Hz), 60.6 (CH), 21.0 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −114.91 (*rac*), −114.94 (*meso*); **HRMS** (ESI Positive) calcd. for $C_{28}H_{26}F_2N_2O_2S$, [M+Na] 515.1575, found 515.1570; Anal. Calc. for $C_{28}H_{26}F_2N_2O_2S$: C, 68.27; H, 5.32; N, 5.69%. Found: C, 68.24; H, 5.33; N, 5.61%; **HPLC**: Daicel Chiralcel OD-H column, 90:10 hexanes:^{i}PrOH; 0.5 mL/min; 200 nm; (*R*,*R*)-enantiomer t_R = 34.6 min, *meso* t_R = 37.8 min, (*S*,*S*)-enantiomer t_R = 41.3 min.

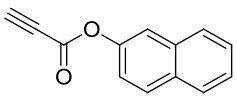
***N*,*N*'-Sulfonyl *bis*-[(*S*)-(4-fluorophenyl)(4-methylphenyl)methanamine] (*S*,*S*)-3.100j**



Prepared from **3.85b** (77.1 mg, 0.25 mmol) and **3.28d** (213 mg, 0.6 mmol) using general method **H**, purified by column chromatography (3:1 pet. ether:EtOAc) to afford the product (94.2 mg, 76%, 91:9 dr, 98% *ee*). Analytical data as for **3.100j** except; $\mathbf{[\alpha]_D}$ = +1.8 (*c* = 0.91, $CHCl_3$, for 91:9 dr, 98% *ee* material); **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.15-7.11 (m, 4H, CH_{aryl}), 7.08-6.98 (m, 8H, CH_{aryl}), 6.96-6.90 (m, 4H, CH_{aryl}), 5.51 (d, *J* = 6.4 Hz, 2H, NHC*H*),

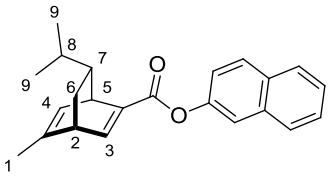
4.64 (d, J = 6.0 Hz, 2H, N*H*CH), 2.30 (s, 6H, $ArCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 162.1 (C, d, $^1J_{CF}$ = 245 Hz), 137.8 (C), 137.7 (C), 137.0 (C, d, $^4J_{CF}$ = 3.0 Hz), 129.5 (CH), 128.8 (CH, d, $^3J_{CF}$ = 7.6 Hz), 127.0 (CH), 115.5 (CH, d, $^2J_{CF}$ = 21.4 Hz), 60.7 (CH), 21.0 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −114.85.

Naphthalen-2-yl propiolate 3.103[172]



Propiolic acid **3.102** (2.37 mL, 38.2 mmol) and DCC (7.88 g, 38.2 mmol) were added to a stirred solution of 2-naphthol (5.0 g, 34.7 mmol) and DMAP (42.3 mg, 0.35 mmol) in CH_2Cl_2 (75 mL). The resulting yellow suspension was allowed to warm to rt and stirred for 5 h. The white precipitate was filtered and the filtrate concentrated *in vacuo*. The residue was purified by column chromatography (19:1 pet. ether:EtOAc) to afford the product as a white solid (5.19 g, 76%); **R_f** 0.33 (19:1 hexanes:EtOAc); **M.p.** 69-70 °C; lit. 71-73 °C;[172] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3299, 2129, 1732, 1192; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.87-7.79 (m, 3H, CH_{aryl}), 7.62 (d, J = 2.8 Hz, 1H, CH_{aryl}), 7.52-7.45 (m, 2H, CH_{aryl}), 7.26 (dd, J = 8.8, 2.4 Hz, 1H, CH_{aryl}), 3.08 (s, 1H, C≡CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 151.0 (C), 147.4 (C), 133.5 (C), 131.7 (C), 129.7 (CH), 127.8 (CH), 127.7 (CH), 126.8 (CH), 126.1 (CH), 120.3 (CH), 118.5 (CH), 76.9 (C), 74.2 (CH); **HRMS** (ESI Positive) calcd. for $C_{13}H_8O_2$, [M+Na] 219.0417, found 219.0411. These data were consistent with literature values.[287]

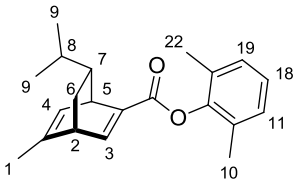
(1*R*,4*R*,7*R*)-Naphthalen-2-yl 7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate (*R*,*R*,*R*)-3.99[172]



Dimethylaluminium chloride (1.0 M in hexanes, 29.4 mL, 29.4 mmol) was added slowly to a stirred solution of naphthalen-2-yl propiolate **3.103** (5.25 g, 26.8 mmol) and (*R*)-α-phelladrene **(*R*)-3.104** (~50% chemical purity, 9.57 mL, 29.4 mmol) in CH_2Cl_2 (70 mL) at –78 °C. The orange solution was stirred and allowed to warm to rt over 24 h. The solution was poured onto

a slurry of ice (50 g) and 2 M HCl (50 mL), this was extracted with CH_2Cl_2 (3 × 50 mL). The organics were washed with brine (2 × 100 mL), dried (Na_2SO_4) and concentrated to a yellow oil. This was purified by column chromatography (19:1 pet. ether:EtOAc) resulting in a yellow oil, which was recrystallised from CH_2Cl_2/hexanes to give a white solid (3.93 g, 44%); $\mathbf{R_f}$ 0.28 (19:1 pet. ether:EtOAc); **M.p.** 89-91 °C (CH_2Cl_2/hexanes); lit. 92-94 °C;[172] $\mathbf{[\alpha]_D}$ = +2.6 (*c* = 1.19, $CHCl_3$; lit.[172] +4.4, *c* = 1.12, $CHCl_3$); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3011, 2962, 1721, 1240, 1157, 1061; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.85-7.77 (m, 3H, CH_{aryl}), 7.60-7.58 (m, 2H, CH^3 and CH_{aryl}), 7.49-7.42 (m, 2H, CH_{aryl}), 7.26 (dd, *J* = 8.8, 2.4 Hz, 1H, CH_{aryl}), 5.89 (dt, *J* = 6.4, 1.6 Hz, 1H, CH^4), 4.21 (dt, *J* = 6.0, 2.0 Hz, 1H, CH^5), 3.48 (dq, *J* = 6.0, 1.6 Hz, 1H, CH^2), 1.87 (d, *J* = 1.6 Hz, 3H, $CH_3{}^1$), 1.66 (ddd, *J* = 12.0, 8.8, 3.2 Hz, 1H, $CH^{6\alpha}$), 1.33-1.27 (m, 1H, CH^7), 1.19-1.10 (m, 1H, CH^8), 1.04 (ddd, *J* = 11.6, 4.8, 2.4 Hz, 1H, $CH^{6\beta}$), overlapped by 1.02 (d, *J* = 6.4 Hz, 3H, $CH_3{}^{9\alpha}$), 0.85 (d, *J* = 6.4 Hz, 3H, $CH_3{}^{9\beta}$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 163.6 (C), 148.7 (C), 148.3 (CH), 143.3 (C), 140.5 (C), 133.8 (C), 131.3 (C), 129.2 (CH), 127.7 (CH), 127.6 (CH), 126.4 (CH), 125.5 (CH), 124.3 (CH), 121.4 (CH), 118.6 (CH), 47.7 (CH), 44.3 (CH), 39.7 (CH), 33.8 (CH), 31.5 (CH_2), 21.9 (CH_3), 21.4 (CH_3), 19.0 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{23}H_{24}O_2$, [M+H] 333.1849, found 333.1835. These data were consistent with literature values.[172]

(1*R*,4*R*,7*R*)-2,6-Dimethylphenyl 7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate (*R*,*R*,*R*)-4.15[172]



(*R*,*R*,*R*)-3.99 (803 mg, 2.42 mmol) was added portionwise to a stirred solution of NaOMe (261 mg, 4.83 mmol) in methanol (10 mL). The suspension was stirred at rt for 16 h, then concentrated to a brown oil and purified by column chromatography (19:1 hexanes:EtOAc) the afford the product as a colourless oil (465 mg, 89%); A solution of the resultant oil (400 mg, 1.82 mmol) and $LiOH.H_2O$ (306 mg, 7.28 mmol) in MeOH (10 mL) and H_2O (3 mL) was stirred at 50 °C for 4 h. Diluted with 2M HCl (10 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was taken

up in CH_2Cl_2 (10 mL) and cooled to 0 °C. 2,6-Dimethylphenol (222 mg, 1.82 mmol, DCC (412 mg, 2.00 mmol) and DMAP (11.0 mg, 91 μmol) were added and the solution stirred at rt for 4 h. The resulting white precipitate was removed by filtration and the filtrate concentrated to a yellow oil. Purification by column chromatography (19:1 hexanes:EtOAc) gave the product as a cream solid (436 mg, 77%); $\mathbf{R_f}$ 0.18 (19:1 hexanes:EtOAc); **M.p.** 78-80 °C; lit. 74-76 °C;[172] $\mathbf{[\alpha]_D}$ = +3.2 (*c* = 1.12, $CHCl_3$; lit.[172] +12.3, *c* = 1.19, $CHCl_3$); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 2962, 1718, 1613, 1473, 1245, 1171; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.56 (dd, *J* = 6.2, 2.2 Hz, 1H, CH^3), 7.07-7.01 (m, 3H, $CH^{11,12}$), 5.86 (app. dt, *J* = 5.9, 1.6 Hz, 1H, CH^4), 4.20 (app. dt, *J* = 6.0, 2.0 Hz, 1H, CH^5), 3.46 (app. dq, *J* = 6.0, 2.5 Hz, 1H, CH^2), 2.13 (s, 6H, CH_3^{10}), 1.86 (d, *J* = 2.0 Hz, 3H, CH_3^1), 1.64 (ddd, *J* = 11.6, 8.6, 2.4 Hz, 1H, $CH^{6\alpha}$), 1.28-1.07 (m, 2H, CH^7 and CH^8), 1.03 (ddd, *J* = 11.6, 4.8, 2.8 Hz, 1H, $CH^{6\beta}$) overlapped by 1.00 (d, *J* = 6.4 Hz, 3H, $CH_3^{9\alpha}$), 0.85 (d, *J* = 6.0 Hz, 3H, $CH_3^{9\beta}$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 162.7 (C), 148.3 (C), 147.9 (CH), 143.3 (C), 140.2 (C), 130.4 (C), 128.4 (CH), 125.5 (CH), 124.1 (CH), 48.0 (CH), 44.2 (CH), 39.7 (CH), 33.8 (CH), 31.5 (CH_2), 21.9 (CH_3), 21.4 (CH_3), 19.0 (CH_3), 16.4 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{21}H_{26}O_2$, [M+H] 311.2006, found 311.1988. These data were consistent with literature values.[172]

Phenyl boroxine 3.28a[288]

Synthesised from phenyl boronic acid using general method **F** to give a white powder; $\mathbf{R_f}$ 0.08 (3:1 pet. ether:EtOAc); **M.p.** 213-214 °C; lit. 214-216 °C;[289] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 1603, 1442, 1368, 1350, 1311; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.25 (d, *J* = 6.8 Hz, 6H, CH_{aryl}), 7.63-7.59 (m, 3H, CH_{aryl}), 7.54-7.50 (m, 6H, CH_{aryl}); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 135.6 (CH), 132.7 (CH), 128.0 (CH), (C-B not seen). These data were consistent with literature values.[288]

4-Fluorophenyl boroxine 3.28b[223]

Synthesised from 4-fluorophenyl boronic acid using general method **F** to give a white powder; $\mathbf{R_f}$ 0.08 (3:1 pet. ether:EtOAc); **M.p.** 261-263 °C; lit. 265-266 °C;[290] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 1598, 1405, 1371, 1349, 1240, 1158, 841; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.21 (dd, *J* = 8.6, 6.2 Hz, 6H, CH_{aryl}), 7.19 (tt, *J* = 8.8, 2.1 Hz, 6H, CH_{aryl}); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C

166.1 (d, $^{1}J_{CF}$ = 251 Hz, C), 138.0 (d, $^{3}J_{CF}$ = 9.2 Hz, CH), 115.3 (d, $^{2}J_{CF}$ = 19.8 Hz, CH), (C-B not seen); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F -105.8. These data were consistent with literature values.[223]

4-Chlorophenyl boroxine 3.28c[223]

Synthesised from 4-chlorophenyl boronic acid using general method **F** to give a white powder; **R_f** 0.08 (3:1 pet. ether:EtOAc); **M.p.** 284-286 °C; lit. 261-262.5;[289] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 1594, 1398, 1366, 1345, 1311, 1088; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.13 (d, *J* = 8.4 Hz, 6H, CH_{aryl}), 7.49 (d, *J* = 8.4 Hz, 6H, CH_{aryl}); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 139.4 (C), 137.0 (CH), 134.9 (CH), 128.4 (CH), (C-B not seen). These data were consistent with literature values.[223]

4-Methylphenyl boroxine 3.28d[291]

Synthesised from 4-methylphenyl boronic acid using general method **F** to give a white powder; **R_f** 0.36 (1:1 pet. ether:EtOAc); **M.p.** 253-257 °C; lit. 246-248 °C;[289] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3010, 1612, 1403, 1348, 1183; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.11 (d, *J* = 8.0 Hz, 6H, CH_{aryl}), 7.30 (d, *J* = 7.6 Hz, 6H, CH_{aryl}), 2.43 (s, 9H, $ArCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 142.9 (C), 135.7 (CH), 128.7 (CH), 21.9 (CH_3) (C-B not seen). These data were consistent with literature values.[291]

2-Methylphenyl boroxine 3.28e[292]

Synthesised from 2-methylphenyl boronic acid using general method **F** to give a white powder; **R_f** 0.15 (3:1 pet. ether:EtOAc); **M.p.** 157-159 °C; lit. 165-166 °C;[292] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3009, 1599, 1441, 1348, 1302; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.22 (dd, *J* = 7.6, 1.6 Hz, 3H, CH_{aryl}), 7.45 (td, *J* = 7.4, 1.7 Hz, 3H, CH_{aryl}), 7.33-7.27 (m, 6H, CH_{aryl}), 2.82 (s, 9H, $ArCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 146.2 (C), 137.2 (CH), 132.2 (CH), 130.6 (CH), 125.2 (CH), 23.1 (CH_3), (C-B not seen). These data were consistent with literature values.[292]

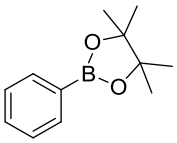
4-Methoxyphenyl boroxine 3.28f[293]

Synthesised from 4-methoxyphenyl boronic acid using general method **F** to give a white powder; $\mathbf{R_f}$ 0.08 (3:1 pet. ether:EtOAc); **M.p.** 205-206 °C; lit. 206-207 °C;[294] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3009, 1603, 1413, 1345, 1313, 1248, 1173, 1011; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.17 (dt, *J* = 8.8, 2.0 Hz, 6H, CH_{aryl}), 7.02 (dt, *J* = 8.8, 2.2 Hz, 6H, CH_{aryl}), 3.90 (s, 9H, OCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 163.2 (C), 137.5 (CH), 113.5 (CH), 55.2 (CH_3), (C-B not seen). These data were consistent with literature values.[293]

4-(Ethoxycarbonyl)phenyl boroxine 3.28g[289]

A flame-dried flask was charged with ethyl 4-iodobenzoate (3.32 mL, 20 mmol) and THF (25 mL) and cooled to –40 °C. *i*-Propylmagnesium bromide (2.0 M in THF, 10 mL, 20 mmol) was added dropwise, stirred at –40 °C for 2.5 h, the solution became dark brown (5.25 mL, 3.0 mmol was removed for preparation of **3.100g**). Cooled to –78 °C and freshly distilled trimethyl borate (3.79 mL, 34 mmol) was added dropwise. The solution was allowed to warm to rt and stirred overnight, the reaction mixture became a viscous yellow suspension. 1 M HCl (40 mL) was added and the mixture was stirred for 2 h at rt. Extracted with Et_2O (2 × 50 mL), the organics were dried (Na_2SO_4) and concentrated to a light yellow solid. The solid was suspended in benzene (25 mL) and stirred at reflux with a Dean-Stark overnight. The white solid was collected by filtration (1.56 g, 52%); $\mathbf{R_f}$ 0.27 (1:1 pet. ether:EtOAc); **M.p.** 150-153 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3214, 1713, 1350, 1280, 1112; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.33 (d, *J* = 8.0 Hz, 6H, CH_{aryl}), 8.21 (d, *J* = 8.4 Hz, 6H, CH_{aryl}), 4.47 (q, *J* = 7.0 Hz, 6H, OCH_2CH_3), 1.48 (t, *J* = 7.2 Hz, 9H, OCH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 166.4 (C), 135.5 (CH), 134.3 (C), 128.9 (CH), 61.3 (CH_2), 14.3 (CH_3), (C-B not seen).

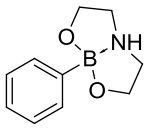
4,4,5,5-Tetramethyl-2-phenyl-1,3,2-dioxaborolane 3.107[295]



A solution of phenyl boronic acid **3.25a** (366 mg, 3 mmol) and pinacol (355 mg, 3 mmol) in Et_2O (12 mL) was stirred at rt for 1.5 h. The solution was concentrated to a light brown oil which crystallised on standing (550 mg, 90%); $\mathbf{R_f}$ 0.77 (1:1 pet. ether:EtOAc); **M.p.** 25-26 °C;

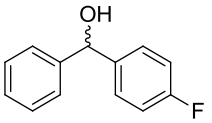
lit. 27-28 °C;[295] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 2983, 1604, 1360, 1144, 1090; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.82-7.80 (m, 2H, CH_{aryl}), 7.46 (tt, *J* = 7.4, 1.7 Hz, 1H, CH_{aryl}), 7.39-7.34 (m, 2H, CH_{aryl}), 1.35 (s, 12H, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 134.7 (CH), 131.2 (CH), 127.7 (CH), 83.8 (C), 24.9 (CH_3), (C-B not seen). These data were consistent with literature values.[295]

4,5,7,8-Tetrahydro-2-(phenyl)-6H-[1,3,6,2]dioxazaborocane 3.108[227]



Diethanolamine (193 µL, 2 mmol) was added to a stirred suspension of phenyl boronic acid **3.25a** (244 mg, 2 mmol) in Et_2O (25 mL). The suspension was stirred at rt for 6 h, the product was collected by filtration as a white powder (371 mg, 97%); **M.p.** 209-211 °C; lit. >200 °C;[227] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 2983, 2871, 1249, 1249, 1083, 1066, 924; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.45-7.42 (m, 2H, CH_{aryl}), 7.20-7.11 (m, 3H, CH_{aryl}), 6.86 (br s, 1H, NH), 3.87 (td, *J* = 9.3, 5.3 Hz, 2H, $OCH_{2\alpha}$), 3.78 (qd, *J* = 6.3, 3.3 Hz, 2H, $OCH_{2\beta}$), 3.08 (tdd, *J* = 9.3, 7.6, 5.3 Hz, 2H, $NHCH_{2\alpha}$), 2.84 (dqd, *J* = 12.0, 3.4, 2.4 Hz, 2H, $NHCH_{2\beta}$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 132.6 (CH), 126.6 (CH), 126.3 (CH), 62.9 (CH_2), 50.7 (CH_2), (C-B not seen). These data were consistent with literature values.[227]

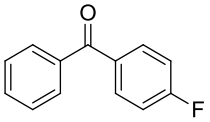
(4-Fluorophenyl)(phenyl)methanol 3.117b[296]



A flame dried Schlenk tube was charged with Et_2O (5 mL) and 4-fluorobenzaldehyde (2.08 mL, 20 mmol) and cooled to 0 °C. Phenylmagnesium bromide (3.0 M in Et_2O, 13.3 mL, 40 mmol) was added dropwise with stirring. The solution was stirred overnight and allowed to warm to rt. The reaction mixture was then quenched with sat. NH_4Cl solution (20 mL), extracted with Et_2O (2 × 20 mL), the organics were dried (Na_2SO_4) and concentrated to a yellow oil. This was purified by column chromatography (3:1 pet. ether:EtOAc) to afford the product as a yellow oil (3.16 g, 78%); **R_f** 0.50 (3:1 pet. ether:EtOAc); **IR** ($CHCl_3$) ν_{max}/cm^{-1}

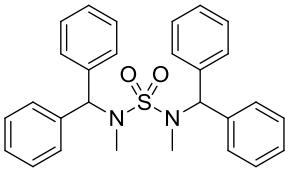
3604, 3010, 1604, 1510, 1157, 1015, 909; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.34-7.24 (m, 7H, CH_{aryl}), 7.00 (tt, *J* = 8.8, 2.5 Hz, 2H, CH_{aryl}), 5.79 (s, 1H, OHC*H*), 2.36 (br s, 1H, O*H*CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 162.1 (C, d, $^{1}J_{CF}$ = 244 Hz), 143.6 (C), 139.5 (C), 128.6 (CH), 128.2 (CH, d, $^{3}J_{CF}$ = 8.7 Hz), 127.7 (CH), 126.4 (CH), 115.2 (CH, d, $^{2}J_{CF}$ = 21.8 Hz), 75.6 (CH); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −115.0; **HRMS** (EI) calcd. for $C_{13}H_{11}FO$, [M^+] 202.0788, found 202.0784. These data were consistent with literature values.[296]

(4-Fluorophenyl)(phenyl)methanone 3.118[297]



Manganese dioxide (27.1 g, 0.31 mol) was added to a solution of (4-fluorophenyl)(phenyl)methanol **3.117c** (3.16 g, 15.6 mmol) in CH_2Cl_2 (100 mL) under argon. The suspension was stirred at rt overnight. The manganese dioxide was removed by filtration through celite, flushing with CH_2Cl_2. The filtrate was concentrated to give the product as a yellow oil (2.40 g, 77 %); **R_f** 0.61 (3:1 pet. ether:EtOAc); **M.p.** 40-43 °C; lit. 43-45 °C;[298] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3011, 1659, 1600, 1506, 1278, 1240, 1156; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.87-7.82 (m, 2H, CH_{aryl}), 7.79-7.76 (m, 2H, CH_{aryl}), 7.60 (tt, *J* = 7.4, 1.6 Hz, 1H, CH_{aryl}), 7.51-7.47 (m, 2H, CH_{aryl}), 7.19-7.13 (m, 2H, CH_{aryl}); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 195.2 (C), 165.4 (C, d, $^{1}J_{CF}$ = 251 Hz), 137.5 (C), 133.8 (C), 132.6 (CH, d, $^{3}J_{CF}$ = 9.2 Hz), 132.4 (CH), 129.8 (CH), 128.3 (CH), 115.4 (CH, d, $^{2}J_{CF}$ = 21.3 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −106.0; **HRMS** (ESI Positive) calcd. for $C_{13}H_9FO$, [M+Na] 223.0530, found 223.0530. These data were consistent with literature values.[297]

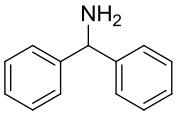
***N,N'*-*Bis*-methyl-*N,N'*-sulfonyl *bis*-[diphenylmethanamine] 3.122**



Sodium hydride (60% w/w in mineral oil) (20.5 mg, 0.513mmol) was added to a stirred solution of **3.100a** (11 mg, 0.233mmol) in THF (10 mL) at 0 °C, and stirred at 0 °C for 1 h. Methyl iodide (32.0 µL, 0.513 mmol) was added at 0 °C, stirred for 18 h and allowed to warm

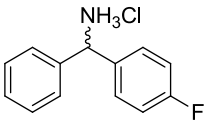
to rt. Partitioned between H_2O (25 mL) and Et_2O (2 × 25 mL). The organics were dried (Na_2SO_4) and concentrated to a light yellow oil. Purification by column chromatography (4:1 pet. ether:EtOAc) gave the product as a white crystalline solid (55.9 mg, 52%); **R_f** 0.56 (4:1 pet. ether:EtOAc); **M.p.** 129-131 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3011, 2927, 1601, 1318, 1161, 946, 832; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.34-7.28 (m, 12H, CH_{aryl}), 7.22-7.19 (m, 8H, CH_{aryl}), 6.41 (s, 2H, $N(CH_3)C\mathit{H}$), 2.57 (s, 6H, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 138.9 (C), 128.8 (CH), 128.4 (CH), 127.5 (CH), 65.0 (CH), 31.2 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{28}H_{28}N_2O_2S$, [M+Na] 479.1764, found 479.1775; Anal. Calc. for $C_{28}H_{28}N_2O_2S$: C, 73.65; H, 6.18; N, 6.14%. Found: C, 73.99; H, 6.58; N, 5.80%.

Diphenylmethanamine 3.40a[299]



Prepared from **3.100a** (85.7 mg, 0.2 mmol) using general method **I**, to afford the product as a colourless oil (69.1 mg, 94%); **R_f** 0.29 (1:1 pet. ether:EtOAc); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3086, 3009, 2970, 1601, 1492, 1452, 904; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.37-7.34 (m, 4H, CH_{aryl}), 7.31-7.27 (m, 4H, CH_{aryl}), 7.20 (tt, J = 7.0, 1.7 Hz, 2H, CH_{aryl}), 5.18 (s, 1H, $NH_2C\mathit{H}$), 1.78 (s, 2H, NH_2); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 145.5 (C), 128.4 (CH), 126.8 (CH), 59.7 (CH) two peaks overlapped. These data were consistent with literature values.[299]

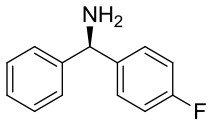
(4-Fluorophenyl)(phenyl)methanamine.hydrogen chloride 3.40b.HCl[144]



Following the procedure of Caballero *et al*.,[300] ammonium acetate (14.8 g, 0.19 mol) and sodium cyanoborohydride (2.41 g, 38.4 mmol) were added to a solution of **3.118** in EtOH (100 mL) and CH_2Cl_2 (5 mL). The suspension was stirred at reflux for 20 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (100 mL) and washed with sat. Na_2CO_3 solution (2 × 100 mL). The organics were dried (Na_2SO_4) and concentrated to a light brown oil (2.60 g). HCl (1.0 M in Et_2O, 13 mL) was added and the resulting white precipitate collected by filtration (1.85 g, 65%); **M.p.** >230 °C dec.; lit. 306-306 °C dec.;[301] **IR** ($CHCl_3$) ν_{max}/cm^{-1}

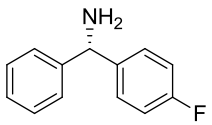
2894, 1602, 1516, 1240; **^{1}H NMR** (400.1 MHz, DMSO-d_6) δ_H 9.15 (br s, 3H, NH_3CH), 7.59-7.56 (m, 2H, CH_{aryl}), 7.54-7.51 (m, 2H, CH_{aryl}), 7.45-7.41 (m, 2H, CH_{aryl}), 7.38-7.34 (m, 1H, CH_{aryl}), 7.30-7.24 (m, 2H, CH_{aryl}), 5.67 (br s, 1H, NH_3CH); **^{13}C NMR** (100.6 MHz, DMSO-d_6) δ_C 161.8 (C, d, $^{1}J_{CF}$ = 244 Hz), 138.1 (C), 134.5 (C, d, $^{4}J_{CF}$ = 3.0 Hz), 129.7 (CH, d, $^{3}J_{CF}$ = 9.1 Hz), 128.8 (CH), 128.3 (CH), 127.2 (CH), 115.6 (CH, d, $^{2}J_{CF}$ = 21.4 Hz), 56.3 (CH); **^{19}F NMR** (376.5 MHz, DMSO-d_6) δ_F −113.7. These data were consistent with literature values.[144]

(*R*)-(4-Fluorophenyl)(phenyl)methanamine (*R*)-3.40b[299]



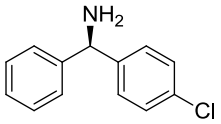
Prepared from **(*R*,*R*)-3.100b** (74.1 mg, 0.15 mmol) using general method **I**, to afford the product as a colourless oil (49.4 mg, 80%, 94% *ee*); **R_f** 0.24 (1:1 pet. ether:EtOAc); **$[\alpha]_D$** = –1.38 (*c* = 1.06, $CHCl_3$, for 94% *ee* material measured on acetamide); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3065, 1604, 1509, 1240, 1157; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.36-7.28 (m, 6H, CH_{aryl}), 7.24-7.20 (m, 1H, CH_{aryl}), 7.00-6.95 (m, 2H, CH_{aryl}), 5.17 (s, 1H, NH_2CH), 1.75 (s, 2H, NH_2CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 161.7 (C, d, $^{1}J_{CF}$ = 244 Hz), 145.4 (C), 141.3 (C, d, $^{4}J_{CF}$ = 3.1 Hz), 128.5 (CH, d, $^{3}J_{CF}$ = 7.6 Hz), 128.3 (CH), 127.0 (CH), 126.7 (CH), 115.1 (CH, d, $^{2}J_{CF}$ = 21.4 Hz), 59.0 (CH); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −116.1; **HRMS** (EI) calcd. for $C_{13}H_{12}FN$, [M^+] 201.0954, found 201.0951. These data were consistent with literature values.[299]

(*S*)-(4-Fluorophenyl)(phenyl)methanamine (*S*)-3.40b[299]



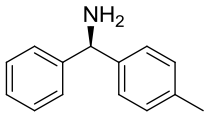
Prepared from **(*S*,*S*)-3.100b** (37.1 mg, 0.08 mmol) using general method **I**, to afford the product as a colourless oil (25.3 mg, 79%, 82% *ee*). Analytical data as for **(*R*)-3.40b** except; **$[\alpha]_D$** = +1.0 (*c* = 1.11, $CHCl_3$, for 82% *ee* material measured on acetamide).

(*R*)-(4-Chlorophenyl)(phenyl)methanamine (*R*)-3.40c[299]



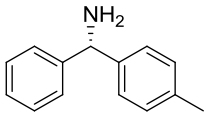
Prepared from **(*R,R*)-3.100c** (63.5 mg, 0.13 mmol) using general method **I**, to afford the product as a yellow oil (51.6 mg, 93%, 87% *ee*); $\mathbf{R_f}$ 0.20 (1:1 pet. ether:EtOAc); $\mathbf{[\alpha]_D}$ = –1.1 (*c* = 1.28, EtOH, for 87% *ee* material (measured on acetamide); lit.[230] –10.9 (*c* = 5.05, EtOH *R* antipode); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3378, 3065, 3011, 1601, 1488, 1091; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.35-7.21 (m, 9H, CH_{aryl}), 5.18 (s, 1H, NH_2CH), 1.74 (s, 2H, NH_2CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 145.2 (C), 144.0 (C), 132.6 (C), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.1 (CH), 126.8 (CH), 59.1 (CH); **HRMS** (EI) calcd. for $C_{13}H_{12}ClN$, [M^+] 217.0658, found 217.0662. These data were consistent with literature values.[299]

(*R*)-(4-Methylphenyl)(phenyl)methanamine (*R*)-3.40d[299]



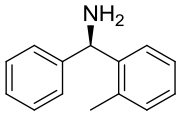
Prepared from **(*R,R*)-3.100d** (48.5 mg, 0.11 mmol) using general method **I**, to afford the product as a yellow oil (30.0 mg, 72%, 92% *ee*); $\mathbf{R_f}$ 0.26 (1:1 pet. ether:EtOAc); $\mathbf{[\alpha]_D}$ = +7.7 (*c* = 0.52, $CHCl_3$, for 92% *ee* material measured on acetamide); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3010, 2966, 2864, 1602, 1513, 1493, 1452, 908; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.38-7.35 (m, 2H, CH_{aryl}), 7.32-7.19 (m, 5H, CH_{aryl}), 7.11 (d, *J* = 7.6 Hz, 2H, CH_{aryl}), 5.17 (s, 1H, NH_2CH), 2.31 (s, 3H, $ArCH_3$), 1.75 (s, 2H, NH_2CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 145.8 (C), 142.7 (C), 136.5 (C), 129.1 (CH), 128.4 (CH), 126.81 (CH), 126.76 (CH), 59.4 (CH) 21.0 (CH_3) two peaks overlapped; **HRMS** (EI) calcd. for $C_{14}H_{15}N$, [M^+] 197.1204, found 197.1199. These data were consistent with literature values.[299]

(*S*)-(4-Methylphenyl)(phenyl)methanamine (*S*)-3.40d[299]



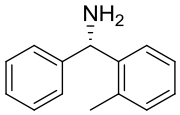
Prepared from **(*S*,*S*)-3.100d** (83.6 mg, 0.18 mmol) using general method **I**, to afford the product as a yellow oil (43.0 mg, 60%, 92% *ee*). Analytical data as for **(*R*)-3.40d** except; $[\alpha]_D$ = –1.7 (*c* = 1.02, $CHCl_3$, for 92% *ee* material measured on acetamide).

(*R*)-(2-Methylphenyl)(phenyl)methanamine (*R*)-3.40e[302]



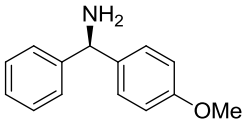
Prepared from **(*R*,*R*)-3.100e** (63.6 mg, 0.14 mmol) using general method **I**, to afford the product as a yellow oil (28.8 mg, 53%, 97% *ee*). Analytical data as for **(*S*)-3.40e** except; $[\alpha]_D$ = –10.2 (*c* = 1.39, $CHCl_3$, for 97% *ee* material measured on acetamide).

(*S*)-(2-Methylphenyl)(phenyl)methanamine (*S*)-3.40e[302]



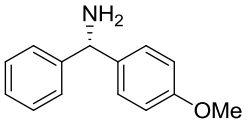
Prepared from **(*S*,*S*)-3.100e** (66.2 mg, 0.15 mmol) using general method **I**, to afford the product as a yellow oil (18.3 mg, 32%, 96% *ee*); $\mathbf{R_f}$ 0.35 (1:1 pet. ether:EtOAc); $[\alpha]_D$ = +11.1 (*c* = 0.92, $CHCl_3$, for 96% *ee* material measured on acetamide); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3066, 3011, 1601, 1491, 1453, 909; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.53 (dd, *J* = 7.8, 1.0 Hz, 1H, CH_{aryl}), 7.29-7.11 (m, 8H, CH_{aryl}), 5.37 (s, 1H, NH_2CH), 2.35 (s, 3H, $ArCH_3$), 1.76 (br s, 2H, NH_2CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 144.9 (C), 143.2 (C), 135.4 (C), 130.5 (CH), 128.4 (CH), 127.3 (CH), 126.8 (CH), 126.1 (CH), 126.0 (CH), 56.1 (CH), 19.5 (CH_3) two peaks overlapped; **HRMS** (EI) calcd. for $C_{14}H_{15}N$, [$\{M-H\}^+$] 196.1126, found 196.1120.

(*R*)-(4-Methoxyphenyl)(phenyl)methanamine (*R*)-3.40f[299]



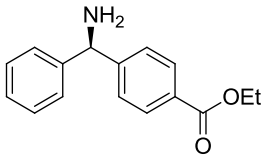
Prepared from **(*R,R*)-3.100f** (78.8 mg, 0.16 mmol) using general method **I**, to afford the product as a colourless oil (65.6 mg, 95%, 86% *ee*). Analytical data as for **(*S*)-3.40f** except; $[\alpha]_D$ = +1.4 (*c* = 1.01, $CHCl_3$, for 86% *ee* material measured on acetamide).

(*S*)-(4-Methoxyphenyl)(phenyl)methanamine (*S*)-3.40f[299]



Prepared from **(*S,S*)-3.100f** (60.9 mg, 0.13 mmol) using general method **I**, to afford the product as a colourless oil (45.4 mg, 85%, 94% *ee*); $\mathbf{R_f}$ 0.18 (1:1 pet. ether:EtOAc); $[\alpha]_D$ = –2.2 (*c* = 1.27, $CHCl_3$, for 94% *ee* material measured on acetamide); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3011, 1612, 1511, 1248, 1034, 838; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.37-7.35 (m, 2H, CH_{aryl}), 7.32-7.26 (m, 4H, CH_{aryl}), 7.21 (tt, *J* = 7.4, 1.8 Hz, 1H, CH_{aryl}), 6.84 (dt, *J* = 8.8, 2.7 Hz, 2H, CH_{aryl}), 5.16 (s, 1H, NH_2CH), 3.77 (s, 3H, OCH_3), 1.75 (br s, 2H, NH_2CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 158.4 (C), 145.8 (C), 137.8 (C), 128.4 (CH), 127.9 (CH), 126.8 (CH), 126.7 (CH), 113.7 (CH), 59.0 (CH), 55.1 (CH_3); **HRMS** (EI) calcd. for $C_{14}H_{15}NO$, [M^+] 213.1154, found 213.1144. These data were consistent with literature values.[299]

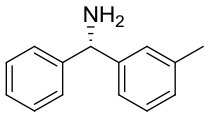
(*R*)-Ethyl 4-(amino(phenyl)methyl)benzoate (*R*)-3.40g



Prepared from **(*R,R*)-3.100g** (60.9 mg, 0.09 mmol) using general method **I**, pyridine removed *in vacuo* and the resulting yellow solid was purified by column chromatography (1:1 pet. ether:EtOAc) to afford the product as a yellow oil (14.6 mg, 31%, 91% *ee*); $\mathbf{R_f}$ 0.11 (1:1 pet. ether:EtOAc); $[\alpha]_D$ = –2.3 (*c* = 0.45, $CHCl_3$, for 91% *ee* material measured on acetamide); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 2985, 2929, 1714, 1282, 1194; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.98 (d, *J*

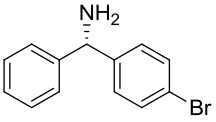
= 8.4 Hz, 2H, CH_{aryl}), 7.36-7.22 (m, 7H, CH_{aryl}), 5.30 (s, 1H, C*H*NH_2), 4.37 (q, *J* = 7.2 Hz, 2H, CH_2), 1.38 (t, *J* = 7.0 Hz, 3H, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 165.9 (C), 141.2 (C), 136.1 (C), 130.8 (C), 130.2 (CH), 129.2 (CH), 129.1 (CH), 127.2 (CH), 126.9 (CH), 61.2 (CH_2), 58.6 (CH), 14.3 (CH_3); **HRMS** (EI) calcd. for $C_{16}H_{17}NO_2$, [M^+] 255.1259, found 255.1250.

(*S*)-(3-Methylphenyl)(phenyl)methanamine (*S*)-3.40h[303]



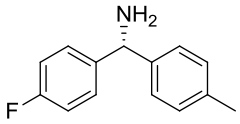
Prepared from **(*S*,*S*)-3.100h** (86.1 mg, 0.19 mmol) using general method **I**, to afford the product as a yellow oil (54.4 mg, 73%, 86% *ee*); **R_f** 0.33 (1:1 pet. ether:EtOAc); **[α]$_D$** = +1.3 (*c* = 1.09, $CHCl_3$, for 86% *ee* material measured on acetamide); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3011, 2964, 1605, 1493, 1453, 883; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.37-7.35 (m, 2H, CH_{aryl}), 7.31-7.27 (m, 2H, CH_{aryl}), 7.22-7.13 (m, 4H, CH_{aryl}), 7.03-7.01 (m, 1H, CH_{aryl}), 5.15 (s, 1H, NH_2CH), 2.31 (s, 3H, $ArCH_3$), 1.76 (br s, 2H, NH_2CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 145.6 (C), 145.5 (C), 138.0 (C), 128.4 (CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 126.8 (CH), 123.9 (CH), 59.6 (CH), 21.4 (CH_3) two peaks overlapped; **HRMS** (ESI) calcd. for $C_{14}H_{15}N$, [M^+] 197.1204, found 197.1200.

(*S*)-(4-Bromophenyl)(phenyl)methanamine (*S*)-3.40i[230]



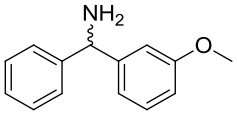
Prepared from **(*S*,*S*)-3.100i** (77.4 mg, 0.13 mmol) using general method **I**, to afford the product as a yellow oil (41.9 mg, 61%, 95% *ee*); **R_f** 0.32 (1:1 pet. ether:EtOAc); **[α]$_D$** = +12.2 (*c* = 0.89, EtOH, for 95% *ee* material measured on acetamide; lit.[171] +9.9 for 98% *ee S* antipode, *c* = 0.62, EtOH); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3065, 1484, 1072, 1026; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.42 (dt, *J* = 8.8, 2.2 Hz, 2H, CH_{aryl}), 7.35-7.20 (m, 7H, CH_{aryl}), 5.16 (s, 1H, NH_2CH), 1.74 (br s, 2H, NH_2CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 145.1 (C), 144.5 (C), 131.5 (CH), 128.6 (CH), 128.5 (CH), 127.1 (CH), 127.8 (CH), 120.7 (C), 59.2 (CH); **HRMS** (ESI Positive) calcd. for $C_{13}H_{12}BrN$, [M-NH_2] 244.9960, found 244.9962.

(*S*)-(4-Fluorophenyl)(4-methylphenyl)methanamine (*S*)-3.40j



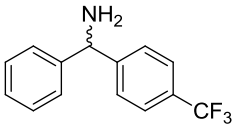
Prepared from **(*S*,*S*)-3.100j** (38.0 mg, 0.07 mmol) using general method **I**, to afford the product as a yellow oil (28.9 mg, 99%, 92% *ee*); $\mathbf{R_f}$ 0.34 (1:1 pet. ether:EtOAc); $\mathbf{[\alpha]_D}$ = +2.9 (*c* = 1.37, $CHCl_3$, for 92% *ee* material measured on acetamide); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3009, 1603, 1509, 1296, 1157; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.40-7.35 (m, 2H, CH_{aryl}), 7.27 (dt, *J* = 8.4, 1.8 Hz, 2H, CH_{aryl}), 7.16 (d, *J* = 7.6 Hz, 2H, CH_{aryl}), 7.02 (tt, *J* = 8.8, 2.4 Hz, 2H, CH_{aryl}), 5.20 (s, 1H, $NH_2C\mathit{H}$), 2.36 (s, 3H, $ArCH_3$), 1.82 (br s, 2H, NH_2); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 161.7 (C, d, $^1J_{CF}$ = 243 Hz), 142.5 (C), 141.4 (C), 136.7 (C), 129.2 (CH), 128.3 (CH, d, $^3J_{CF}$ = 7.3 Hz), 126.6 (CH), 115.1 (CH, d, $^2J_{CF}$ = 20.3 Hz), 58.8 (CH), 21.0 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −116.2; **HRMS** (EI) calcd. for $C_{14}H_{14}FN$, [M^+] 215.1105, found 215.1111.

(3-Methoxyphenyl)(phenyl)methanamine (±)-3.40k



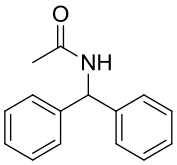
Prepared from **(±)-4.2dak** (109.3 mg, 0.31 mmol) using general method **I**, to give a yellow oil (49.1 mg, 73%); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3375, 3005, 2963, 1599, 1488, 1454, 1260, 1048; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.38-7.35 (m, 2H, CH_{aryl}), 7.31-7.27 (m, 2H, CH_{aryl}), 7.24-7.19 (m, 2H, CH_{aryl}), 6.96-6.93 (m, 2H, CH_{aryl}), 6.77-6.74 (m, 1H, CH_{aryl}), 5.16 (s, 1H, $NH_2C\mathit{H}$), 3.76 (s, 3H, OCH_3), 1.77 (br s, 2H, $N\mathit{H}_2CH$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 159.7 (C), 147.2 (C), 145.4 (C), 129.4 (CH), 128.4 (CH), 126.9 (CH), 126.8 (CH), 119.2 (CH), 112.5 (CH), 112.1 (CH), 59.6 (CH), 55.1 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{14}H_{15}NO$, [M-NH_2] 197.0966, found 197.0987. This compound is reported in the literature but no analytical data are quoted.[304]

(4-(Trifluoromethyl)phenyl)(4-methylphenyl)methanamine (±)-3.40l



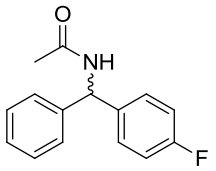
Prepared from **(±)-4.2dal** (75.7 mg, 0.2 mmol) using general method **I** to give the product as a colourless oil (48.6 mg, 99%); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 2964, 1620, 1416, 1326, 1261, 1168, 1018; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.49-7.42 (m, 4H, CH_{aryl}), 7.29-7.22 (m, 4H, CH_{aryl}), 7.18-7.14 (m, 1H, CH_{aryl}), 5.18 (s, 1H, $NH_2C\mathit{H}$), 1.70 (br s, 2H, $N\mathit{H}_2CH$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 149.5 (C), 144.8 (C), 129.2 (C, q, $^2J_{CF}$ = 32.1 Hz), 128.7 (CH), 127.3 (CH), 127.2 (CH), 126.8 (CH), 125.4 (CH, q, $^3J_{CF}$ = 3.7 Hz), 124.2 (C, q, $^1J_{CF}$ = 270 Hz), 59.5 (CH); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −62.4; **HRMS** (EI) calcd. for $C_{14}H_{12}F_3N$, [M^+] 251.0916, found 251.0926. These data were consistent with literature values.[151]

***N*-Benzhydrylacetamide 3.128a**[305]



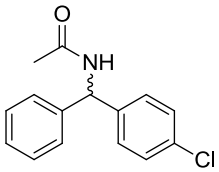
Prepared from **3.40a** (75 mg, 0.175 mmol) using general method **J** to give the product as a white solid (60.3 mg, 77%); **R_f** 0.26 (1:1 pet. ether:EtOAc); **M.p.** 143-145 °C; lit. 147-148 °C;[305] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3442, 3010, 1673, 1496; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.35-7.22 (m, 10H, CH_{aryl}), 6.25 (d, *J* = 8.0 Hz, 1H, NHC*H*), 6.05 (d, *J* = 6.8 Hz, 1H, N*H*CH), 2.07 (s, 3H, $(CO)CH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.2 (C), 141.5 (C), 128.5 (CH), 127.4 (CH), 127.3 (CH), 56.9 (CH), 23.1 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{15}H_{15}NO$, [M+Na] 248.1046, found 248.1037. These data were consistent with literature values.[305]

***N*-((4-Fluorophenyl)(phenyl)methyl)acetamide 3.128b**[306]



Prepared from **3.40b.HCl** (14.4 mg, 0.06 mmol) using general method **J** (4 equiv. pyridine used) to give a white solid (8.9 mg, 61%); $\mathbf{R_f}$ 0.24 (1:1 pet. ether:EtOAc); **M.p.** 147-149 °C; lit. 152-153 °C;[306] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3442, 3011, 1674, 1509, 1239; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.36-7.26 (m, 3H, CH_{aryl}), 7.21-7.15 (m, 4H, CH_{aryl}), 7.04-6.98 (m, 2H, CH_{aryl}), 6.22 (d, *J* = 8.0 Hz, 1H, NHC*H*), 6.07 (d, *J* = 7.6 Hz, 1H, N*H*CH), 2.05 (s, 3H, (CO)CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.4 (C), 161.8 (C, d, $^1J_{CF}$ = 245 Hz), 141.3 (C), 137.3 (C, d, $^4J_{CF}$ = 4.6 Hz), 129.0 (CH, d, $^3J_{CF}$ = 7.6 Hz), 128.5 (CH), 127.4 (CH), 127.3 (CH), 115.2 (CH, d, $^2J_{CF}$ = 21.3 Hz), 56.2 (CH), 22.8 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −115.1; **HRMS** (ESI Positive) calcd. for $C_{15}H_{14}FNO$, [M+Na] 266.0952, found 266.0953; **HPLC**: Daicel Chiralcel OD column, 90:10 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 8.8 min, (*R*)-enantiomer t_R = 13.6 min. These data were consistent with literature values.[306]

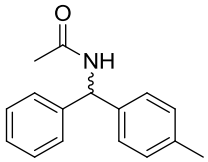
***N*-((4-Chlorophenyl)(phenyl)methyl)acetamide 3.128c**[307]



4-Chlorobenzhydrylamine hydrochloride (385 mg, 1.53 mmol) was partitioned between EtOAc and 2 M $NaOH_{(aq)}$, the organics were dried (Na_2SO_4) and concentrated to a yellow oil (333.4 mg, 1.53 mmol). This oil was taken up in CH_2Cl_2 (5 mL), pyridine (247 µL, 3.06 mmol) and acetyl chloride (120 µL, 1.68 mmol) were added and the solution stirred overnight. The solution was diluted with CH_2Cl_2 (20 mL) and washed with sat. $NaHCO_3$ solution (2 × 20 mL) and 2 M HCl (2 × 20 mL), dried (Na_2SO_4) and concentrated to an orange oil. Purification by column chromatography (3:1 pet. ether:EtOAc) gave the product as a white solid (280 mg, 71%); $\mathbf{R_f}$ 0.18 (1:1 pet. ether:EtOAc); **M.p.** 126-128 °C; lit. 133-135 °C;[307] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3442, 3009, 1674, 1494; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.36-7.28 (m, 5H, CH_{aryl}),

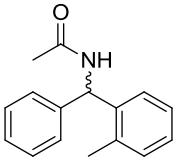
7.21-7.15 (m, 4H, CH_{aryl}), 6.21 (d, *J* = 8.0 Hz, 1H, NHC*H*), 6.00 (d, *J* = 7.2 Hz, 1H, N*H*CH), 2.07 (s, 3H, (CO)CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.1 (C), 141.0 (C), 140.0 (C), 133.3 (C), 128.8 (CH), 128.8 (CH), 128.7 (CH), 127.8 (CH), 127.5 (CH), 56.5 (CH), 23.3 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{15}H_{14}ClNO$, [M+Na] 282.0656, found 282.0657; **HPLC**: Daicel Chiralcel OD column, 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 20.2 min, (*R*)-enantiomer t_R = 33.6 min. These data were consistent with literature values.[307]

***N*-((4-Methylphenyl)(phenyl)methyl)acetamide 3.128d**[308]



Prepared from **3.40d** (79.1 mg, 0.173 mmol) using general method **J** to give the product as a cream solid (62.9 mg, 76%); **R_f** 0.25 (1:1 pet. ether:EtOAc); **M.p.** 126-128 °C; lit. 129-131 °C;[308] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3442, 3011, 1673, 1497; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.33-7.20 (m, 5H, CH_{aryl}), 7.13-7.08 (m, 4H, CH_{aryl}), 6.20 (br s, 2H, overlapped N*H*CH and NHC*H*), 2.31 (s, 3H, $ArCH_3$), 2.01 (s, 3H, (CO)CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.0 (C), 141.7 (C), 138.6 (C), 137.1 (C), 129.3 (CH), 128.5 (CH), 127.3 (CH), 127.2 (CH), 56.7 (CH), 23.3 (CH_3), 21.0 (CH_3) two peaks overlapped; **HRMS** (ESI Positive) calcd. for $C_{16}H_{17}NO$, [M+H] 240.1383, found 240.1377; **HPLC**: Daicel Chiralcel OD-H column, 90:10 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 8.0 min, (*R*)-enantiomer t_R = 10.1 min. These data were consistent with literature values.[308]

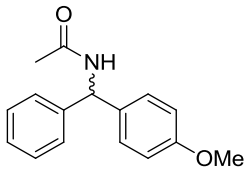
***N*-((2-Methylphenyl)(phenyl)methyl)acetamide 3.128e**[308]



Prepared from **3.40e** (44.1 mg, 0.097 mmol) using general method **J** to give the product as a cream solid (40.3 mg, 87%); **R_f** 0.41 (1:1 pet. ether:EtOAc); **M.p.** 130-132 °C; lit. 147-155 °C;[308] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3442, 3011, 1673, 1497; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.32-

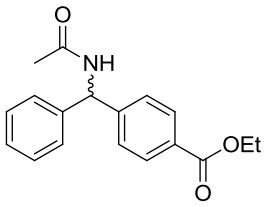
7.09 (m, 9H, CH_{aryl}), 6.40 (d, *J* = 8.0 Hz, 1H, NHC*H*), 6.08 (br d, *J* = 6.8 Hz, 1H, N*H*CH), 2.29 (s, 3H, $ArCH_3$), 2.03 (s, 3H, $(CO)CH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 168.9 (C), 141.0 (C), 139.5 (C), 136.3 (C), 130.8 (CH), 128.6 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 126.6 (CH), 126.1 (CH), 54.0 (CH), 23.2 (CH_3), 23.4 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{16}H_{17}NO$, [M+Na] 262.1202, found 262.1193; **HPLC**: Daicel Chiralpak AD-H and Chiralpak AD columns in series (total column length = 50 cm), 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 27.6 min, (*R*)-enantiomer t_R = 32.0 min. These data were consistent with literature values.[308]

***N*-((4-Methoxyphenyl)(phenyl)methyl)acetamide 3.128f**[305]



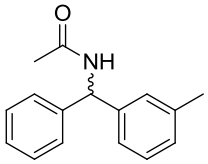
Prepared from **3.40f** (89.3 mg, 0.183 mmol) using general method **J** to give the product as a cream solid (65.2 mg, 70%); **R_f** 0.21 (1:1 pet. ether:EtOAc); **M.p.** 154-156 °C; lit. 158.5 °C;[305] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3442, 3010, 1672, 1512, 1250, 1034; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.35-7.30 (m, 2H, CH_{aryl}), 7.28-7.21 (m, 3H, CH_{aryl}), 7.16-7.12 (m, 2H, CH_{aryl}), 6.88-6.84 (dm, *J* = 8.8 Hz, 2H, CH_{aryl}), 6.21 (d, *J* = 8.0 Hz, 1H, NHC*H*), 5.97 (br d, *J* = 8.4 Hz, 1H, N*H*CH), 3.79 (s, 3H, OCH_3), 2.06 (s, 3H, $(CO)CH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.0 (C), 158.9 (C), 141.7 (C), 133.7 (C), 128.62 (CH), 128.58 (CH), 127.3 (CH), 127.2 (CH), 114.0 (CH), 56.4 (CH), 55.3 (CH_3), 23.4 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{16}H_{17}NO_2$, [M+Na] 278.1151, found 278.1135; **HPLC**: Daicel Chiralcel OD column, 90:10 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 14.2 min, (*R*)-enantiomer t_R = 16.6 min. These data were consistent with literature values.[305]

Ethyl 4-(acetamido(phenyl)methyl)benzoate 3.128g



Prepared from **3.40g** (92.4 mg, 0.161 mmol) using general method **J** to give the product as a colourless oil (72.7 mg, 85%); $\mathbf{R_f}$ 0.33 (1:1 pet. ether:EtOAc); **M.p.** 100-102 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3442, 3011, 1713, 1676, 1496, 1280, 1109; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.00 (dm, *J* = 8.8 Hz, 2H, CH_{aryl}), 7.36-7.28 (m, 5H, CH_{aryl}), 7.22-7.20 (m, 2H, CH_{aryl}), 6.61 (br d, *J* = 7.6 Hz, 1H, N*H*CH), 6.28 (d, *J* = 8.8 Hz, 1H, NHC*H*), 4.37 (q, *J* = 7.1 Hz, 2H, $COOCH_2$), 2.06 (s, 3H, $(CO)CH_3$), 1.40 (t, *J* = 7.2 Hz, 3H, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.4 (C), 166.2 (C), 146.4 (C), 140.8 (C), 129.8 (CH), 129.5 (C), 128.8 (CH), 127.8 (CH), 127.5 (CH), 127.2 (CH), 60.9 (CH_2), 56.9 (CH), 23.1 (CH_3), 14.3 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{18}H_{19}NO_3$, [M+Na] 320.1257, found 320.1246; Anal. Calc. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71%. Found: C, 72.68; H, 6.45; N, 4.66%; **HPLC**: Daicel Chiralcel OD column, 90:10 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 14.3 min, (*R*)-enantiomer t_R = 18.5 min.

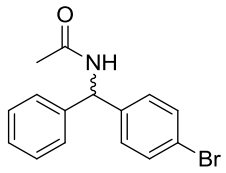
***N*-((3-Methylphenyl)(phenyl)methyl)acetamide 3.128h**[303]



Prepared from **3.40h** (69.7 mg, 0.153 mmol) using general method **J** to give the product as a white solid (45.1 mg, 62%); $\mathbf{R_f}$ 0.23 (1:1 pet. ether:EtOAc); **M.p.** 99-101 °C; lit. 97 °C;[303] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3443, 3010, 1673, 1497; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.34-7.19 (m, 6H, CH_{aryl}), 7.09-7.00 (m, 3H, CH_{aryl}), 6.20 (d, *J* = 8.0 Hz, 1H, NHC*H*), 6.12 (br d, *J* = 8.0 Hz, 1H, N*H*CH), 2.32 (s, 3H, $ArCH_3$), 2.04 (s, 3H, $(CO)CH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.0 (C), 141.6 (C), 141.4 (C), 138.3 (C), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.1 (CH), 127.4 (CH), 127.3 (CH), 124.4 (CH), 56.9 (CH), 23.4 (CH_3), 21.4 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{16}H_{17}NO$, [M+Na] 262.1202, found 262.1191; **HPLC**: Daicel Chiralpak

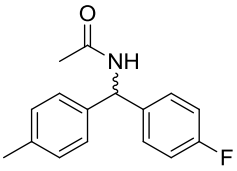
AD-H and Chiralpak AD columns in series (total column length = 50 cm), 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 31.2 min, (*R*)-enantiomer t_R = 35.4 min. These data were consistent with literature values.[303]

***N*-((2-Bromophenyl)(phenyl)methyl)acetamide 3.128i**[307]



Prepared from **3.40i** (67.6 mg, 0.115 mmol) using general method **J** to give the product as a cream solid (59.6 mg, 85%); $\mathbf{R_f}$ 0.36 (1:1 pet. ether:EtOAc); **M.p.** 143-147 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3442, 3010, 1676, 1495, 1030; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.43 (dm, *J* = 8.4 Hz, 2H, CH_{aryl}), 7.34-7.26 (m, 3H, CH_{aryl}), 7.19-7.16 (m, 2H, CH_{aryl}), 7.09 (dm, *J* = 8.4 Hz, 2H, CH_{aryl}), 6.28 (br d, *J* = 7.6 Hz, 1H, N*H*CH), 6.16 (d, *J* = 8.0 Hz, 1H, NHC*H*), 2.01 (s, 3H, (CO)CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.2 (C), 140.9 (C), 140.5 (C), 131.6 (CH), 129.0 (CH), 128.8 (CH), 127.7 (CH), 127.4 (CH), 121.3 (C), 56.5 (CH), 23.2 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{15}H_{14}BrNO$, [M+Na] 326.0151, found 326.0138; Anal. Calc. for $C_{15}H_{14}BrNO$: C, 59.23; H, 4.64; N, 4.60%. Found: C, 59.14; H, 4.66; N, 4.30%; **HPLC**: Daicel Chiralcel OD column, 90:10 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 10.8 min, (*R*)-enantiomer t_R = 15.1 min. These data were consistent with literature values.[307]

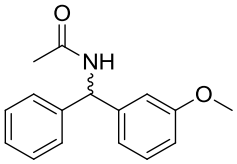
***N*-((4-Fluorophenyl)(4-methylphenyl)methyl)acetamide 3.128j**



Prepared from **3.40j** (88 mg, 0.179 mmol) using general method **J** to give the product as a cream solid (80.4 mg, 87%); $\mathbf{R_f}$ 0.28 (1:1 pet. ether:EtOAc); **M.p.** 135-137 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3442, 3010, 1674, 1509, 1240; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.24-7.16 (m, 4H, CH_{aryl}), 7.12 (d, *J* = 8.4 Hz, 2H, CH_{aryl}), 7.03 (tt, *J* = 8.8, 2.5 Hz, 2H, CH_{aryl}), 6.21 (d, *J* = 7.6 Hz, 1H, NHC*H*), 6.12 (br d, *J* = 8.0 Hz, 1H, N*H*CH), 2.37 (s, 3H, ArCH_3), 2.07 (s, 3H, (CO)CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.0 (C), 162.0 (C, d, $^{1}J_{CF}$ = 244 Hz), 138.3

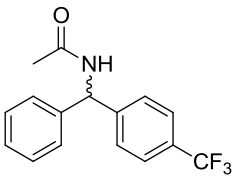
(C), 137.5 (C, d, $^4J_{CF}$ = 3.1 Hz), 137.4 (C), 129.4 (CH), 128.9 (CH, d, $^3J_{CF}$ = 7.6 Hz), 127.3 (CH), 115.4 (CH, d, $^2J_{CF}$ = 21.3 Hz), 56.1 (CH), 23.3 (CH_3), 21.0 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F -115.3; **HRMS** (ESI Positive) calcd. for $C_{16}H_{16}FNO$, [M+H] 258.1289, found 258.1279; **HPLC**: Daicel Chiralcel OD-H and Chiralcel OD columns in series (total column length = 50 cm), 95:5 hexanes:^{i}PrOH; 0.5 mL/min; 200 nm; (*S*)-enantiomer t_R = 72.1 min, (*R*)-enantiomer t_R = 80.8 min.

***N*-((3-Methoxyphenyl)(phenyl)methyl)acetamide 3.128k**



Prepared from **4.2dak** (110 mg, 0.32 mmol) using general method **J**, purified by column chromatography (1:1 pet. ether:EtOAc) to give the product as a white crystalline solid (54.9 mg, 68%); $\mathbf{R_f}$ 0.20 (1:1 pet. ether:EtOAc); **M.p.** 98-101 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3442, 3008, 1673, 1494, 1260, 995; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.31-7.19 (m, 6H, CH_{aryl}), 6.80-6.77 (m, 3H, CH_{aryl}), 6.49 (d, *J* = 8.0 Hz, 1H, N*H*CH), 6.17 (d, *J* = 8.4 Hz, 1H, NHC*H*), 3.73 (s, 3H, OCH_3), 1.97 (s, 3H, $(CO)CH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.1 (C), 159.7 (C), 143.1 (C), 141.4 (C), 129.6 (CH), 128.5 (CH), 127.4 (CH), 127.3 (CH), 119.7 (CH), 113.4 (CH), 112.4 (CH), 56.9 (CH), 55.1 (CH_3), 23.2 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{16}H_{17}NO_2$, [M+Na] 278.1151, found 278.1147; Anal. Calc. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49%. Found: C, 75.30; H, 6.71; N, 5.49%; **HPLC**: Daicel Chiralpak OD-H, 90:10 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 13.7 min, (*R*)-enantiomer t_R = 27.9 min. This compound is reported in the literature but no analytical data are quoted.[204]

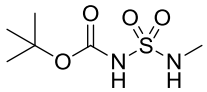
***N*-((4-(Trifluoromethyl)phenyl)(phenyl)methyl)acetamide 3.128l**



Prepared from **4.2dal** (112 mg, 0.29 mmol) using general method **J**, purified by column chromatography (1:1 pet. ether:EtOAc) to give a white solid (64 mg, 75%); $\mathbf{R_f}$ 0.23 (4:1 pet.

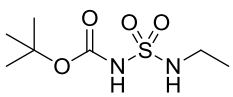
ether:EtOAc); **M.p.** 125-127 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3441, 3011, 1676, 1496, 1326, 1169, 1130; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.54 (d, *J* = 8.0 Hz, 2H, CH_{aryl}), 7.33-7.25 (m, 5H, CH_{aryl}), 7.18-7.16 (m, 2H, CH_{aryl}), 6.67 (br d, *J* = 7.6 Hz, 1H, N*H*CH), 6.22 (d, *J* = 7.6 Hz, 1H, NHC*H*), 1.97 (s, 3H, (CO)CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.5 (C), 145.5 (C), 140.6 (C), 129.5 (C, q, $^2J_{CF}$ = 32.5 Hz), 128.8 (CH), 127.8 (CH), 127.5 (CH), 125.4 (CH, q, $^3J_{CF}$ = 3.4 Hz), 124.0 (C, q, $^1J_{CF}$ = 270 Hz), 56.7 (CH), 23.0 (CH_3), two peaks overlapped; **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −62.5; **HRMS** (ESI Positive) calcd. for $C_{16}H_{14}F_3NO$, [M+Na] 316.0920, found 316.0912; **HPLC**: Daicel Chiralpak OD-H, 90:10 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 6.6 min, (*R*)-enantiomer t_R = 11.0 min. These data were consistent with literature values.[309]

***tert*-Butyl *N*-methylsulfamoylcarbamate 4.10a**[247]



Prepared from methylamine (40 wt. % in H_2O, 51.8 mL, 0.6 mol) using general method **L** to afford the product as a white crystalline solid (17.2 g, 82%); **R_f** 0.50 (5% MeOH/CH_2Cl_2); **M.p.** 144 °C dec.; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3690, 3399, 3296, 2985, 1737, 1602, 1438, 1145; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.33 (br s, 1H, N*H*Boc), 5.22 (app. d, *J* = 4.8 Hz, 1H, N*H*CH_3), 2.76 (d, *J* = 5.2 Hz, 3H, NHC*H*$_3$), 1.50 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 150.2 (C), 83.9 (C), 29.8 (CH_3), 28.0 (CH_3); **HRMS** (ESI Positive) calcd. for $C_6H_{14}N_2O_4S$, [M+Na] 233.0566, found 233.0569; Anal. Calc. for $C_6H_{14}N_2O_4S$: C, 34.28; H, 6.71; N, 13.32%. Found: C, 34.06; H, 6.64; N, 13.21%. These data were consistent with literature values.[310,247]

***tert*-Butyl *N*-ethylsulfamoylcarbamate 4.10b**

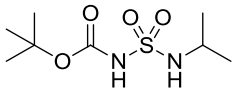


Prepared from ethylamine (70 wt. % in H_2O, 4.85 mL, 0.6 mol) using general method **L** to afford the product as a white crystalline solid (2.11 g, 94%).

Prepared from ethylamine.HCl (1.03 g, 12.6 mmol) using general method **M** to afford the product as a white crystalline solid (2.78 g, 98%).

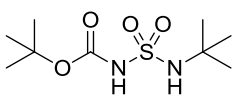
R_f 0.69 (10% MeOH/CH_2Cl_2); **M.p.** 125-127 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3400, 2985, 1737, 1435, 1403, 1144; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.34 (br s, 1H, N*H*Boc), 5.19 (t, *J* = 5.6 Hz, 1H, N*H*CH_2CH_3), 3.14 (dq, *J* = 6.0, 7.2 Hz, 2H, NHC*H*$_2CH_3$), 1.50 (s, 9H, C(C*H*$_3$)$_3$), 1.23 (t, *J* = 7.2 Hz, 3H, $NHCH_2CH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 150.2 (C), 83.8 (C), 38.9 (CH_2), 28.0 (CH_3), 14.5 (CH_3); **HRMS** (ESI Positive) calcd. for $C_7H_{16}N_2O_2S$, [M+Na] 247.0723, found 247.0719; Anal. Calc. for $C_7H_{16}N_2O_2S$: C, 37.49; H, 7.19; N, 12.49%. Found: C, 37.34; H, 7.16; N, 12.33%.

***tert*-Butyl *N*-isopropylsulfamoylcarbamate 4.10c**



Prepared from isopropylamine (4.91 mL, 60 mmol) using general method **L** to afford the product as a white crystalline solid after recrystallisation from ethanol (1.50 g, 63%); **R_f** 0.73 (10% MeOH/CH_2Cl_2); **M.p.** 147 °C dec. (ethanol); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3399, 2983, 1737, 1434, 1404, 1143; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.18 (br s, 1H, N*H*Boc), 4.96 (d, *J* = 6.8 Hz, 1H, N*H*CH$(CH_3)_2$), (app. sextet, *J* = 6.6 Hz, 1H, C*H*$(CH_3)_2$), 1.50 (s, 9H, C(C*H*$_3$)$_3$), 1.23 (d, *J* = 6.4 Hz, 6H, CH(C*H*$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 150.2 (C), 83.7 (C), 47.1 (CH), 28.0 (CH_3), 23.1 (CH_3); **HRMS** (ESI Positive) calcd. for $C_8H_{18}N_2O_4S$, [M+Na] 261.0879, found 261.0882; Anal. Calc. for $C_8H_{18}N_2O_4S$: C, 40.32; H, 7.61; N, 11.76%. Found: C, 40.30; H, 7.59; N, 11.70%. These data were consistent with literature values.[311]

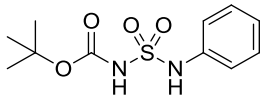
***tert*-Butyl *N*-*tert*-butylsulfamoylcarbamate 4.10d**



Prepared from *tert*-butylamine (12.6 mL, 120 mmol) using general method **L** to give a white solid (4.51 g, 89%); **R_f** 0.69 (5% MeOH/CH_2Cl_2); **M.p.** 151 °C dec.; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3401, 2939, 1737, 1435, 1403, 1143; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.11 (s, 1H, N*H*Boc), 5.03 (s, 1H, N*H*C$(CH_3)_3$)), 1.50 (s, 9H, COOC(C*H*$_3$)$_3$), 1.36 (s, 9H, NHC(C*H*$_3$)$_3$); **^{13}C NMR**

(100.6 MHz, $CDCl_3$) δ_C 150.2 (C), 83.5 (C), 55.0 (C), 29.4 (CH_3), 28.1 (CH_3); **HRMS** (ESI Positive) calcd. for $C_9H_{20}N_2O_4S$, [M+Na] 275.1036, found 275.1042; Anal. Calc. for $C_9H_{20}N_2O_4S$: C, 42.84; H, 7.99; N, 11.10%. Found: C, 42.62; H, 7.97; N, 11.05%.

***tert*-Butyl *N*-phenylsulfamoylcarbamate 4.10e**

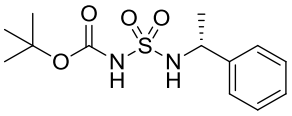


Prepared from aniline (10.9 mL, 120 mmol) using general method **L** to give a white solid (4.37 g, 80%).

Prepared from aniline (1.82 mL, 20 mmol) using general method **M** to afford the product as a cream crystalline solid (4.23 g, 78%).

R_f 0.67 (10% MeOH/CH_2Cl_2); **M.p.** 140 °C dec.; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3395, 1739, 1432, 1145; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.38-7.34 (m, 2H, CH_{aryl}), 7.28-7.23 (m, 3H, CH_{aryl}), 7.15 (br s, 1H, N*H*Boc), 7.01 (br s, 1H, N*H*C$(CH_3)_3$), 1.45 (s, 9H, C(C*H*$_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 149.9 (C), 135.8 (C), 129.5 (CH), 126.6 (CH), 122.9 (CH), 84.2 (C), 27.9 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{11}H_{16}N_2O_4S$, [M+Na] 295.0723, found 295.0720; Anal. Calc. for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29%. Found: C, 48.13; H, 5.84; N, 10.26%. These data were consistent with literature values.[248]

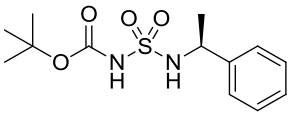
(*R*)-*tert*-Butyl *N*-(1-phenylethyl)sulfamoylcarbamate (*R*)-4.10g



Prepared from (*R*)-1-methylbenzylamine (2.54 mL, 20 mmol) using general method **M** to give a white solid (3.29 g, 55%); **R_f** 0.66 (5% MeOH/CH_2Cl_2); **M.p.** 142 °C dec.; **$[\alpha]_D$** = +1.8 (*c* = 1.11, $CHCl_3$); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3399, 2984, 1738, 1433, 1145; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.37-7.26 (m, 5H, CH_{aryl}), 7.13 (s, 1H, N*H*Boc), 5.55 (d, *J* = 7.2 Hz, 1H, N*H*CH), 4.61-4.54 (m, 1H, NHC*H*), 1.53 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.39 (s, 9H, C(C*H*$_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 149.9 (C), 141.6 (C), 128.8 (CH), 127.9 (CH), 126.2 (CH), 83.5 (C), 54.5 (CH), 27.9 (CH_3), 23.1 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{13}H_{20}N_2O_4S$, [M+Na]

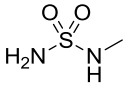
323.1036, found 323.1022; Anal. Calc. for $C_{13}H_{20}N_2O_4S$: C, 51.98; H, 6.71; N, 9.33%. Found: C, 51.97; H, 6.73; N, 9.23%.

(*S*)-*tert*-Butyl *N*-(1-phenylethyl)sulfamoylcarbamate (*S*)-4.10g



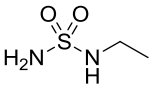
Prepared from (*S*)-1-methylbenzylamine (2.58 mL, 20 mmol) using general method **M** to give a white solid (3.50 g, 58%). Analytical data as for **(*R*)-4.10g** except; $[\alpha]_D$ = −1.3 (*c* = 0.99, $CHCl_3$).

***N*-Methylsulfamide 4.4a**



Prepared from **4.10a** (16.7 g, 79.5 mmol) using general method **N**, purified by column chromatography (5% MeOH/CH_2Cl_2) to give the product as a white crystalline solid (7.28 g, 83%); $\mathbf{R_f}$ 0.24 (10:1 CH_2Cl_2:MeOH); **M.p.** 63-64 °C; lit. 63-65 °C;[312] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3446, 3396, 3351, 1403, 1344, 1162; **^{1}H NMR** (400.1 MHz, acetone-d_6) δ_H 5.81 (br s, 2H, NH_2), 5.51 (br s, 1H, N*H*CH_3), 2.71 (d, *J* = 5.2 Hz, 3H, NHC*H*$_3$); **^{13}C NMR** (100.6 MHz, methanol-d_4) δ_C 29.6 (CH_3); **HRMS** (EI) calcd. for $CH_6N_2O_2S$, [M^+] 110.0150, found 110.0150; Anal. Calc. for $CH_6N_2O_2S$: C, 10.91; H, 5.49; N, 25.44%. Found: C, 10.97; H, 5.36; N, 25.16%. These data were consistent with literature values.[312,313]

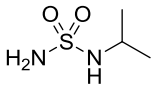
***N*-Ethylsulfamide 4.4b**



Prepared from **4.10b** (2.0 g, 8.92 mmol) using general method **N**, purified by column chromatography (10% MeOH/CH_2Cl_2) to give the product as a white crystalline solid (1.10 g, 99%); $\mathbf{R_f}$ 0.12 (5% MeOH/CH_2Cl_2); **IR** (neat) ν_{max}/cm^{-1} 3285, 2983, 1561, 1428, 1326, 1159, 954; **^{1}H NMR** (400.1 MHz, DMSO-d_6) δ_H 6.42 (br s, 3H, NH_2 and N*H*CH_2), 2.90 (q, *J* = 7.3 Hz, 2H, NHC*H*$_2$CH$_3$), 1.06 (t, *J* = 7.4 Hz, 3H, NHCH$_2$C*H*$_3$); **^{13}C NMR** (100.6 MHz, DMSO-

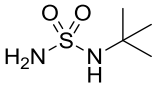
d$_6$) δ_C 37.4 (CH_2), 14.7 (CH_3); **HRMS** (ESI Positive) calcd. for $C_2H_8N_2O_2S$, [M+Na] 147.0199, found 147.0198. These data were consistent with literature values.[314]

***N*-*iso*-Propylsulfamide 4.4c**



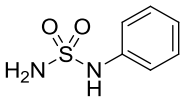
Prepared from **4.10c** (1.95 g, 8.17 mmol) using general method **N**, purified by column chromatography (5% MeOH/CH_2Cl_2) to give the product as a pale yellow oil (788 mg, 70%); **R$_f$** 0.26 (5% MeOH/CH_2Cl_2); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3433, 3386, 3345, 3297, 2977, 1550, 1343, 1141, 1006, 910; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 4.87 (br s, 3H, NH_2 and N*H*CH), 3.62 (septet, *J* = 6.5 Hz, 1H, NHC*H*), 1.24 (d, *J* = 6.4 Hz, 6H, CH(C*H*$_3$)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 46.5 (CH), 23.5 (CH_3); **HRMS** (EI) calcd. for $C_3H_{10}N_2O_2S$, [M-Me$^+$] 123.0223, found 123.0228; This compound is reported in the literature but no analytical data are quoted.[315]

***N*-*tert*-Butylsulfamide 4.4d**[316]



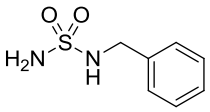
Prepared from **4.10d** (9.94 g, 39.4 mmol) using general method **N**, no chromatography required to give a colourless crystalline solid (5.70 g, 95%); **R$_f$** 0.16 (5% MeOH/CH_2Cl_2); **M.p.** 52-54 °C; lit. 57-59 °C;[316] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3386, 2979, 1416, 1337, 1151, 996; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 6.40 (br s, 2H, NH_2), 6.30 (br s, 1H, N*H*C(CH_3)$_3$), 1.24 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 52.3 (C), 29.6 (CH_3); **HRMS** (EI) calcd. for $C_4H_{12}N_2O_2S$, [M-Me$^+$] 137.0379, found 137.0383. These data were consistent with literature values.[316,317]

***N*-Phenylsulfamide 4.4e**[318]



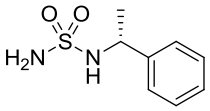
Prepared from **4.10e** (4.32 g, 15.5 mmol) using general method **N**, purified by column chromatography (5% MeOH/CH_2Cl_2) to give the product as a light brown solid (2.12 g, 79%);.**R_f** 0.22 (5% MeOH/CH_2Cl_2); **M.p.** 105-107 °C; lit. 108.5-109.5 °C;[318] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3350, 1412, 1164; **^{1}H NMR** (400.1 MHz, DMSO-d_6) δ_H 9.46 (s, 1H, N*H*Ph), 7.28-7.23 (m, 2H, CH_{aryl}), 7.17-7.14 (m, 2H, CH_{aryl}), 7.06 (br s, 2H, NH_2) 6.96 (tt, *J* = 7.2, 1.1 Hz, 1H, CH_{aryl}); **^{13}C NMR** (100.6 MHz, DMSO-d_6) δ_C 139.5 (C), 128.7 (CH), 121.8 (CH), 117.9 (CH); **HRMS** (EI) calcd. for $C_6H_8N_2O_2S$, [M^+] 172.0301, found 172.0305. These data were consistent with literature values.[318]

***N*-Benzylsulfamide 4.4f**[319]



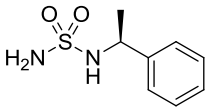
Following the procedure of Kohn *et al.*[243] a solution of benzylamine (5.47 mL, 50 mmol) and sulfamide (4.81 g, 50 mmol) in H_2O (50 mL) was stirred at reflux for 5 h. The resulting suspension was allowed to cool with stirring. The white solid was collected by filtration, washed with H_2O and dried on the pump (6.10 g, 66%). **R_f** 0.34 (1:1 pet. ether:EtOAc); **M.p.** 103-105 °C; lit. 104-105 °C;[319] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3348, 1414, 1349, 1162; **^{1}H NMR** (400.1 MHz, DMSO-d_6) δ_H 7.36-7.30 (m, 4H, CH_{aryl}), 7.26-7.22 (m, 1H, CH_{aryl}), 7.03 (t, *J* = 6.4 Hz, 1H, N*H*CH_2), 6.61 (s, 2H, NH_2), 4.07 (d, *J* = 6.4 Hz, 2H, NHC*H*$_2$Ph); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 138.7 (C), 128.1 (CH), 127.6 (CH), 126.9 (CH), 46.1 (CH_2); **HRMS** (ESI Positive) calcd. for $C_7H_{10}N_2O_2S$, [M+Na] 209.0355, found 209.0364. These data were consistent with literature values.[319]

(*R*)-*N*-(1-Phenylethyl)sulfamide (*R*)-4.4g



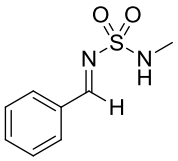
Prepared from **(*R*)-4.10g** (1.39 g, 4.63 mmol) using general method **N**, purified by column chromatography (2:1 pet. ether:EtOAc) to give a colourless oil (1.59 g, 80%); $\mathbf{R_f}$ 0.11 (2:1 pet. ether:EtOAc); $\mathbf{[\alpha]_D}$ = +19.1 (*c* = 1.22, $CHCl_3$); **IR** (Liquid film) ν_{max}/cm^{-1} 3283, 1603, 1495, 1455, 1331, 1163, 967; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.36-7.24 (m, 5H, CH_{aryl}), 5.23 (br d, *J* = 5.6 Hz, 1H, N*H*CH), 4.59-4.53 (m, 3H, NH_2 and NHC*H*), 1.50 (d, *J* = 6.4 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 142.5 (C), 128.8 (CH), 127.7 (CH), 126.3 (CH), 54.0 (CH), 23.3 (CH_3); **HRMS** (ESI Positive) calcd. for $C_8H_{12}N_2O_2S$, [M+H] 223.0512, found 223.0523. These data were consistent with literature values.[317]

(*S*)-*N*-(1-Phenylethyl)sulfamide (*S*)-4.4g



Prepared from **(*S*)-4.4g** (1.50 g, 5.00 mmol) using general method **N**, purified by column chromatography (2:1 pet. ether:EtOAc) to give a colourless oil (1.59 g, 73%); Analytical data as for **(*R*)-4.4g** except; $\mathbf{[\alpha]_D}$ = −23.5 (*c* = 1.26, $CHCl_3$).

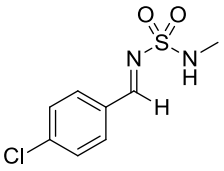
***N*-Methyl-*N*'-[phenylmethylidene]sulfamide 4.1aa**



Prepared from **4.4a** (3.30 g, 30 mmol) and benzaldehyde (3.37 mL, 33 mmol) using general method **O**, trituration with hexanes gave the product as a cream solid (5.09 g, 86%); $\mathbf{R_f}$ 0.19 (4:1 pet. ether:EtOAc); **M.p.** 127-130 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3386, 1610, 1578, 1336, 1161, 842; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.93 (s, 1H, N=CH), 7.96-7.93 (m, 2H, CH_{aryl}), 7.64 (tt, *J* = 1.6, 7.4 Hz, 1H, CH_{aryl}), 7.55-7.51 (m, 2H, CH_{aryl}), 4.42 (d, *J* = 5.2 Hz, 1H, N*H*CH_3), 2.84 (d, *J* = 5.2 Hz, 3H, NHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 170.0 (CH), 134.6 (CH), 132.3 (C), 130.9 (CH), 129.2 (CH), 29.9 (CH_3); **HRMS** (ESI Positive) calcd. for $C_8H_{10}N_2O_2S$,

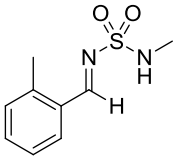
[M+Na] 221.0355, found 221.0359; Anal. Calc. for $C_8H_{10}N_2O_2S$: C, 48.47; H, 5.08; N, 14.13%. Found: C, 48.28; H, 5.14; N, 13.99%.

***N*-Methyl-*N*'-[4-chlorophenylmethylidene]sulfamide 4.1ba**



Prepared from **4.4a** (1.10 g, 10 mmol) and 4-chlorobenzaldehyde (1.55 g, 11 mmol) using general method **O**, purified by column chromatography (2:1 pet. ether:EtOAc) to give a white solid (1.60 g, 67%); $\mathbf{R_f}$ 0.23 (2:1 pet. ether:EtOAc); **M.p.** 135-137 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3388, 1611, 1594, 1338, 1162, 842; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.88 (s, 1H, N=CH), 7.88 (dt, *J* = 8.4, 2.3 Hz, 2H, CH_{aryl}), 7.50 (dt, *J* = 8.4, 2.2 Hz, 2H, CH_{aryl}), 4.44 (br q, *J* = 5.2 Hz, 1H, NH), 2.84 (q, *J* = 5.2 Hz, 3H, CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 168.5 (CH), 141.1 (C), 132.0 (CH), 130.8 (C), 129.6 (CH), 29.9 (CH_3); **HRMS** (ESI Positive) calcd. for $C_8H_9N_2O_2S$, [M+Na] 254.9965, found 254.9974; Anal. Calc. for $C_8H_9N_2O_2S$: C, 41.29; H, 3.90; N, 12.04%. Found: C, 41.24; H, 3.86; N, 11.82%.

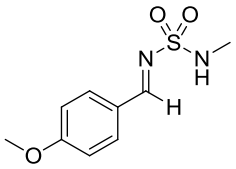
***N*-Methyl-*N*'-[2-methylphenylmethylidene]sulfamide 4.1ae**



Prepared from **4.4a** (552 mg, 5 mmol) and *o*-tolualdehyde (0.64 mL, 5.5 mmol) using general method **O**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (665 mg, 63%); $\mathbf{R_f}$ 0.10 (4:1 pet. ether:EtOAc); **M.p.** 124-127 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3389, 1611, 1593, 1403, 1355, 1161, 843; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 9.23 (s, 1H, N=CH), 8.03 (dd, *J* = 8.0, 1.2 Hz, 1H, CH_{aryl}), 7.50 (td, *J* = 7.4, 1.3 Hz, 1H, CH_{aryl}), 7.34-7.28 (m, 2H, CH_{aryl}), 4.38 (q, *J* = 5.2 Hz, 1H, N*H*CH_3), 2.84 (d, *J* = 5.6 Hz, 3H, NHC*H*$_3$), 2.62 (s, 3H, ArCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 168.5 (CH), 141.8 (C), 134.2 (CH), 131.6 (CH), 130.3 (C), 130.2 (CH), 126.6 (CH), 29.9 (CH_3), 19.7 (CH_3); **HRMS** (ESI Positive) calcd. for

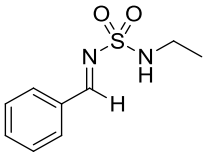
$C_9H_{12}N_2O_2S$, [M+Na] 235.0512, found 235.0505; Anal. Calc. for $C_9H_{12}N_2O_2S$: C, 50.92; H, 5.70; N, 13.20%. Found: C, 50.70; H, 5.64; N, 13.16%.

***N*-Methyl-*N*'-[4-methoxyphenylmethylidene]sulfamide 4.1af**



Prepared from **4.4a** (551 mg, 5 mmol) and *p*-anisaldehyde (668 μL, 5.5 mmol) using general method **O**, purified by column chromatography (2:1 pet. ether:EtOAc) to give a white solid (743 mg, 65%); $\mathbf{R_f}$ 0.15 (2:1 pet. ether:EtOAc); **M.p.** 114-116 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3386, 1599, 1569, 1514, 1333, 1263, 1157, 840; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.84 (s, 1H, N=CH), 7.89 (dt, *J* = 9.2, 2.3 Hz, 2H, CH_{aryl}), 7.00 (dt, *J* = 8.8, 2.0 Hz, 2H, CH_{aryl}), 4.39 (q, *J* = 5.3 Hz, 1H, N*H*CH_3), 3.90 (s, 3H, OCH_3), 2.81 (d, *J* = 5.6 Hz, 3H, NHC*H*$_3$); **^{13}C NMR** (125.8 MHz, $CDCl_3$) δ_C 169.2 (CH), 165.0 (C), 133.3 (CH), 125.0 (C), 114.7 (CH), 55.7 (CH_3), 29.9 (CH_3); **HRMS** (ESI Positive) calcd. for $C_9H_{12}N_2O_3S$, [M+Na] 251.0461, found 251.0460; Anal. Calc. for $C_9H_{12}N_2O_3S$: C, 47.35; H, 5.30; N, 12.27%. Found: C, 47.11; H, 5.27; N, 12.29%.

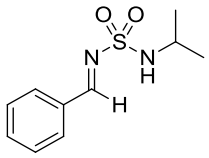
***N*-Ethyl-*N*'-[phenylmethylidene]sulfamide 4.1ba**



Prepared from **4.4b** (1.99 g, 16 mmol) and benzaldehyde (1.80 g, 17.7 mmol) using general method **O**, to give a cream solid which was triturated with hexanes to give the product as a white solid (2.93 g, 86%); $\mathbf{R_f}$ 0.23 (4:1 pet. ether:EtOAc); **M.p.** 76-80 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3380, 2985, 1611, 1337, 1160, 863; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.92 (s, 1H, N=CH), 7.95-7.92 (m, 2H, CH_{aryl}), 7.63 (tt, *J* = 7.4, 1.5 Hz, 1H, CH_{aryl}), 7.54-7.50 (m, 2H, CH_{aryl}), 4.41 (t, *J* = 5.8 Hz, 1H, N*H*CH_2CH_3), 3.22 (dq, *J* = 7.2, 6.0 Hz, 2H, NHC*H*$_2$$CH_3$), 1.24 (t, *J* = 7.4 Hz, 3H, CH_2C*H*$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.4 (CH), 134.5 (CH), 132.4 (C), 130.9 (CH), 129.2 (CH), 38.9 (CH_2), 15.3 (CH_3); **HRMS** (ESI Positive) calcd. for

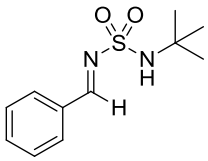
$C_9H_{12}N_2O_2S$, [M+Na] 235.0512, found 235.0523; Anal. Calc. for $C_9H_{12}N_2O_2S$: C, 50.92; H, 5.70; N, 13.20%. Found: C, 50.68; H, 5.72; N, 13.02%.

***N*-*iso*-Propyl-*N*'-[phenylmethylidene]sulfamide 4.1ca**



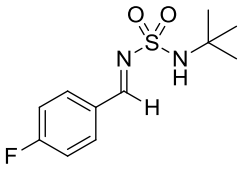
Prepared from **4.4c** (584 mg, 4.23 mmol) and benzaldehyde (475 μL, 4.65 mmol) using general method **O**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white crystalline solid (859 mg, 90%); $\mathbf{R_f}$ 0.20 (4:1 pet. ether:EtOAc); **M.p.** 52-55 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3380, 2978, 1611, 1577, 1341, 1159, 1003; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.92 (s, 1H, N=CH), 7.94-7.91 (m, 2H, CH_{aryl}), 7.63 (tt, *J* = 7.6, 1.6 Hz, 1H, CH_{aryl}), 7.53-7.49 (m, 2H, CH_{aryl}), 4.44 (d, *J* = 8.0 Hz, 1H, N*H*CH$(CH_3)_2$), (doublet of septets, *J* = 7.6, 6.4 Hz, 1H, NHC*H*$(CH_3)_2$), 1.26 (d, *J* = 6.4 Hz, 6H, CH(C*H*$_3)_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 168.6 (CH), 134.4 (CH), 132.5 (C), 130.8 (CH), 129.1 (CH), 47.1 (CH), 23.9 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{10}H_{14}N_2O_2S$, [M+Na] 249.0668, found 249.0666.

***N*-*tert*-Butyl-*N*'-[phenylmethylidene]sulfamide 4.1da**



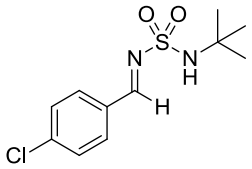
Prepared from **4.4d** (1.14 g, 7.5 mmol) and benzaldehyde (0.84 mL, 8.25 mmol) using general method **O**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (1.49 g, 83%); $\mathbf{R_f}$ 0.33 (4:1 pet. ether:EtOAc); **M.p.** 103-106 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3386, 2980, 1613, 1576, 1391, 1333, 1150, 998, 864; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.92 (s, 1H, N=CH), 7.93-7.91 (m, 2H, CH_{aryl}), 7.62 (tt, *J* = 7.4, 1.5 Hz, 1H, CH_{aryl}), 7.53-7.49 (m, 2H, CH_{aryl}), 4.50 (s, 1H, N*H*C$(CH_3)_3$)), 1.39 (s, 9H, C$(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 167.8 (CH), 134.2 (CH), 132.7 (C), 130.7 (CH), 129.1 (CH), 55.0 (C), 30.2 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{11}H_{16}N_2O_2S$, [M+Na] 263.0825, found 263.0815; Anal. Calc. for $C_{11}H_{16}N_2O_2S$: C, 54.98; H, 6.71; N, 11.66%. Found: C, 54.82; H, 6.68; N, 11.71%.

***N*-*tert*-Butyl-*N*'-[4-fluorophenylmethylidene]sulfamide 4.1db**



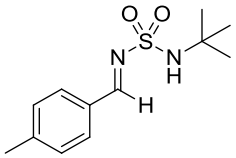
Prepared from **4.4d** (1.14 g, 7.5 mmol) and 4-fluorobenzaldehyde (0.88 ml, 8.25 mmol) using general method **O**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford product as a cream solid (1.15 g, 59%); $\mathbf{R_f}$ 0.31 (4:1 pet. ether:EtOAc); **M.p.** 103-105 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3386, 2939, 1601, 1510, 1333, 1242, 1149, 999; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.88 (s, 1H, N=CH), 7.96-7.91 (m, 2H, CH_{aryl}), 7.22-7.17 (m, 2H, CH_{aryl}), 4.63 (s, 1H, N*H*C$(CH_3)_3$)), 1.39 (s, 9H, C(C*H*$_3$)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 166.4 (C, d, $^1J_{CF}$ = 256 Hz), 166.3 (CH), 133.1 (CH, d, $^3J_{CF}$ = 10.2 Hz), 129.0 (C), 116.6 (CH, d, $^2J_{CF}$ = 21.8 Hz), 55.0 (C), 30.1 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −102.5; **HRMS** (ESI Positive) calcd. for $C_{11}H_{15}FN_2O_2S$, [M+Na] 281.0730, found 281.0724; Anal. Calc. for $C_{11}H_{15}FN_2O_2S$: C, 51.15; H, 5.85; N, 10.84%. Found: C, 51.10; H, 5.85; N, 10.84%.

***N*-*tert*-Butyl-*N*'-[4-chlorophenylmethylidene]sulfamide 4.1dc**



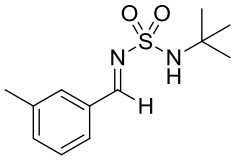
Prepared from **4.4d** (1.40 g, 9.2 mmol) and 4-chlorobenzaldehyde (1.42 g, 10.1 mmol) using general method **O**, purified by column chromatography (4:1 pet. ether:EtOAc) to give the product as a white solid (1.21 g, 85%); $\mathbf{R_f}$ 0.32 (4:1 pet. ether:EtOAc); **M.p.** 111-114 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3386, 2980, 1614, 1595, 1334, 1150, 999, 868; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.87 (s, 1H, N=CH), 7.85 (dt, *J* = 8.4, 2.1 Hz, 2H, CH_{aryl}), 7.49 (dt, *J* = 8.4, 2.0 Hz, 2H, CH_{aryl}), 4.46 (s, 1H, N*H*C$(CH_3)_3$)), 1.39 (s, 9H, C$(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 166.4 (CH), 140.7 (C), 131.8 (CH), 131.1 (C), 129.6 (CH), 55.1 (C), 30.2 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{11}H_{15}ClN_2O_2S$, [M+Na] 297.0435, found 297.0441; Anal. Calc. for $C_{11}H_{15}ClN_2O_2S$: C, 48.08; H, 5.50; N, 10.20%. Found: C, 48.05; H, 5.48; N, 10.21%.

***N*-*tert*-Butyl-*N*'-[4-methylphenylmethylidene]sulfamide 4.1dd**



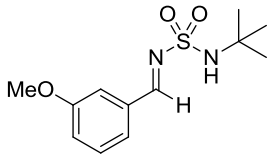
Prepared from **4.4d** (1.14 g, 7.5 mmol) and *p*-tolualdehyde (0.98 ml, 8.25 mmol) using general method **O**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford product as a cream solid (1.69 g, 88%); $\mathbf{R_f}$ 0.39 (4:1 pet. ether:EtOAc); **M.p.** 131-134 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3386, 2979, 1603, 1569, 1332, 1148, 998, 872; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.87 (s, 1H, N=CH), 7.81 (d, *J* = 8.0 Hz, 2H, CH_{aryl}), 7.31 (d, *J* = 8.0 Hz, 2H, CH_{aryl}), 4.38 (br s, 1H, N*H*C$(CH_3)_3$)), 2.45 (s, 3H, ArCH_3), 1.38 (s, 9H, C$(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 167.7 (CH), 145.5 (C), 130.8 (CH), 130.1 (C), 129.9 (CH), 54.9 (C), 30.1 (CH_3), 21.9 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{12}H_{18}N_2O_2S$, [M+Na] 277.0981, found 277.0982; Anal. Calc. for $C_{12}H_{18}N_2O_2S$: C, 56.67; H, 7.13; N, 11.01%. Found: C, 56.70; H, 7.13; N, 10.92%.

***N*-*tert*-Butyl-*N*'-[3-methylphenylmethylidene]sulfamide 4.1dh**



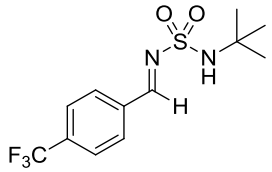
Prepared from **4.4d** (1.14 g, 7.5 mmol) and *m*-tolualdehyde (0.97 mL, 8.25 mmol) using general method **O**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a cream solid (1.44 g, 76%); $\mathbf{R_f}$ 0.26 (4:1 pet. ether:EtOAc); **M.p.** 85-88 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3386, 2937, 1583, 1391, 1333, 1149, 997; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.88 (s, 1H, N=CH), 7.73-7.69 (m, 2H, CH_{aryl}), 7.44-7.37 (m, 2H, CH_{aryl}), 4.51 (br s, 1H, NH), 2.42 (s, 3H, ArCH_3), 1.39 (s, 9H, C$(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 168.1 (CH), 139.0 (C), 135.2 (CH), 132.6 (C), 130.9 (CH), 129.0 (CH), 128.2 (CH), 55.0 (C), 30.2 (CH_3), 21.2 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{12}H_{18}N_2O_2S$, [M+H] 277.0981, found 277.0989; Anal. Calc. for $C_{12}H_{18}N_2O_2S$: C, 56.67; H, 7.13; N, 11.01%. Found: C, 56.58; H, 7.13; N, 11.01%.

***N*-*tert*-Butyl-*N*'-[3-methoxyphenylmethylidene]sulfamide 4.1dk**



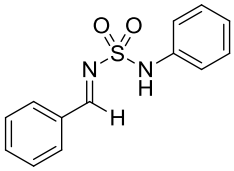
Prepared from **4.4d** (1.14 g, 7.5 mmol) and 3-methoxybenzaldehyde (1.00 ml, 8.25 mmol) using general method **O**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford product as a cream solid (1.80 g, 89%); $\mathbf{R_f}$ 0.26 (4:1 pet. ether:EtOAc); **M.p.** 90-93 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3386, 2941. 1581, 1333, 1150, 998, 869; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.87 (s, 1H, N=CH), 7.48-7.39 (m, 3H, CH_{aryl}), 7.16 (ddd, *J* = 8.0, 2.8, 1.6 Hz, 1H, CH_{aryl}), 4.57 (br s, 1H, N*H*C$(CH_3)_3$)), 3.87 (s, 3H, OCH_3), 1.39 (s, 9H, C$(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 167.8 (CH), 160.1 (C), 134.0 (C), 130.1 (CH), 124.4 (CH), 121.1 (CH), 113.4 (CH), 55.5 (CH_3), 55.0 (C), 30.1 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{12}H_{18}N_2O_3S$, [M+Na] 293.0930, found 293.0927; Anal. Calc. for $C_{12}H_{18}N_2O_3S$: C, 53.31; H, 6.71; N, 10.36%. Found: C, 53.26; H, 6.67; N, 10.24%.

***N*-*tert*-Butyl-*N*'-[4-(trifluoromethyl)phenylmethylidene]sulfamide 4.1dl**



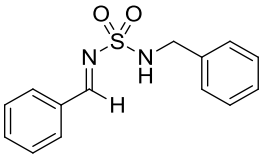
Prepared from **4.4d** (1.14 g, 7.5 mmol) and 4-(trifluoromethyl)benzaldehyde (1.13 mL, 8.25 mmol) using general method **O**, purified by column chromatography (2:1 pet. ether:EtOAc) to give the product as a yellow solid (1.93 g, 84%); $\mathbf{R_f}$ 0.27 (4:1 pet. ether:EtOAc); **M.p.** 103-106 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3386, 2980, 1619, 1324, 1175, 1151, 1000; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.96 (s, 1H, N=CH), 8.04 (d, *J* = 8.0 Hz, 2H, CH_{aryl}), 7.77 (d, *J* = 8.0 Hz, 2H, CH_{aryl}), 4.68 (s, 1H, N*H*C$(CH_3)_3$), 1.40 (s, 9H, C(C*H*$_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 166.1 (CH), 135.7 (C), 135.3 (C, q, $^2J_{CF}$ = 32.8 Hz), 130.7 (CH), 126.1 (CH, q, $^3J_{CF}$ = 3.8 Hz), 123.4 (C, q, $^1J_{CF}$ = 271 Hz), 55.2 (C), 30.1 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −63.3; **HRMS** (ESI Positive) calcd. for $C_{12}H_{15}F_3N_2O_2S$, [M+Na] 331.0699, found 331.0689; Anal. Calc. for $C_{12}H_{15}F_3N_2O_2S$: C, 46.75; H, 4.90; N, 9.09%. Found: C, 46.70; H, 4.88; N, 8.97%.

***N*-Phenyl-*N*'-[phenylmethylidene]sulfamide 4.1ea**



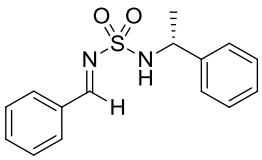
Prepared from **4.4e** (941 mg, 5.5 mmol) and benzaldehyde (0.61 ml, 6.0 mmol) using general method **O**, purified by column chromatography (4:1 pet. ether:EtOAc) to give the product as a cream solid (1.21 g, 85%); $\mathbf{R_f}$ 0.16 (4:1 pet. ether:EtOAc); **M.p.** 112-114 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3363, 3263, 3045, 1600, 1349, 1160, 932; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.83 (s, 1H, N=CH), 7.85-7.83 (m, 2H, CH_{aryl}), 7.59 (tt, *J* = 7.4, 1.4 Hz, 1H, CH_{aryl}), 7.45 (t, *J* = 7.6 Hz, 2H, CH_{aryl}), 7.32-7.24 (m, 4H, CH_{aryl}), 7.16-7.12 (m, 1H, CH_{aryl}), 6.98 (s, 1H, N*H*Ph); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 170.7 (CH), 136.3 (C), 134.8 (CH), 132.0 (C), 131.1 (CH), 129.3 (CH), 129.1 (CH), 125.5 (CH), 121.9 (CH); **HRMS** (ESI Positive) calcd. for $C_{13}H_{12}N_2O_2S$, [M+Na] 283.0512, found 283.0512; Anal. Calc. for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76%. Found: C, 59.90; H, 4.61; N, 10.76%.

***N*-Benzyl-*N*'-[phenylmethylidene]sulfamide 4.1fa**



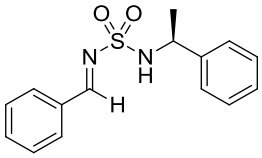
Prepared from **4.4f** (2.12 g, 11.4 mmol) and benzaldehyde (1.28 mL, 12.5 mmol) using general method **O**, to give a cream solid which was triturated with hexanes to give the product as a white solid (2.05 g, 65%); $\mathbf{R_f}$ 0.66 (1:1 pet. ether:EtOAc); **M.p.** 101-103 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3383, 3045, 1611, 1575, 1341, 1158; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.89 (s, 1H, N=CH), 7.90-7.88 (m, 2H, CH_{aryl}), 7.64 (tt, *J* = 7.4, 1.5 Hz, 1H, CH_{aryl}), 7.54-7.49 (m, 2H, CH_{aryl}), 7.37-7.23 (m, 5H, CH_{aryl}), 4.71 (t, *J* = 6.0 Hz, 1H, N*H*CH_2), 4.36 (d, *J* = 6.0 Hz, 2H, NHC*H*$_2$Ph); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 169.6 (CH), 136.2 (C), 134.5 (CH), 132.2 (C), 130.9 (CH), 129.0 (CH), 128.6 (CH), 128.0 (CH), 127.9 (CH), 47.9 (CH_2); **HRMS** (ESI Positive) calcd. for $C_{14}H_{14}N_2O_2S$, [M+Na] 297.0668, found 297.0664; Anal. Calc. for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21%. Found: C, 61.00; H, 5.15; N, 10.10%.

(*R*)-*N*-(1-Phenylethyl)-*N*'-[phenylmethylidene]sulfamide (*R*)-4.1ga



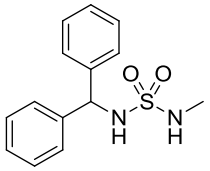
Prepared from **(*R*)-4.4g** (1.24 g, 6.17 mmol) and benzaldehyde (0.69 ml, 6.79 mmol) using general method **O**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford product as a light yellow oil (1.49 g, 83%); $\mathbf{R_f}$ 0.19 (4:1 pet. ether:EtOAc); $\mathbf{[\alpha]_D}$ = +11.8 (*c* = 1.67, $CHCl_3$); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3279, 2979, 1610, 1574, 1332, 1156; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.65 (s, 1H, N=CH), 7.73-7.70 (m, 2H, CH_{aryl}), 7.58 (tt, *J* = 7.4, 1.5 Hz, 1H, CH_{aryl}), 7.46-7.42 (m, 2H, CH_{aryl}), 7.31-7.28 (m, 2H, CH_{aryl}), 7.24-7.19 (m, 2H, CH_{aryl}), 7.10 (tt, *J* = 7.4, 1.5 Hz, 1H, CH_{aryl}), 5.00 (d, *J* = 7.6 Hz, 1H, N*H*CH), 4.66 (quintet, *J* = 7.2 Hz, 1H, NHC*H*), 1.58 (d, *J* = 6.8 Hz, 3H, CHCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 168.9 (CH), 141.6 (C), 134.3 (CH), 132.3 (C), 130.7 (CH), 128.9 (CH), 128.6 (CH), 127.6 (CH), 126.3 (CH), 54.4 (CH), 23.4 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{15}H_{16}N_2O_2S$, [M+Na] 311.0825, found 311.0815.

(*S*)-*N*-(1-Phenylethyl)-*N*'-[phenylmethylidene]sulfamide (*S*)-4.1ga



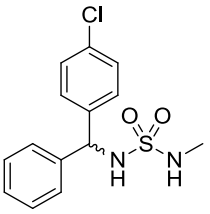
Prepared from **(*S*)-4.4g** (1.45 g, 7.25 mmol) and benzaldehyde (0.81 ml, 7.97 mmol) using general method **O**, purified by column chromatography (4:1 pet. ether:EtOAc) to afford product as a light yellow oil (1.86 g, 89%). Analytical data as for **(*R*)-4.1ga** except: $\mathbf{[\alpha]_D}$ = −13.4 (*c* = 1.36, $CHCl_3$).

***N*-Methyl-*N*'-diphenylmethylsulfonamide 4.2aaa**



Prepared from **4.1aa** (496 mg, 2.5 mmol) using general method **P**, purification by column chromatography (2:1 pet. ether:EtOAc) gave the product as a white crystalline solid (652 mg, 94%); $\mathbf{R_f}$ 0.25 (2:1 pet. ether:EtOAc); **M.p.** 131-133 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3393, 3012, 1409, 1329, 1154, 1028; **^{1}H NMR** (400.1 MHz, acetone-d_6) δ_H 7.45-7.42 (m, 4H, CH_{aryl}), 7.36-7.31 (m, 4H, CH_{aryl}), 7.25 (tt, J = 7.2, 1.5 Hz, 2H, CH_{aryl}), 6.84 (br d, J = 8.4 Hz, 1H, N*H*CH), 5.68 (br q, J = 5.2 Hz, 1H, N*H*CH_3), 5.61 (d, J = 9.2 Hz, 1H, NHC*H*), 2.39 (d, J = 5.2 Hz, 3H, NHC*H*$_3$); **^{13}C NMR** (100.6 MHz, acetone-d_6) δ_C 143.6 (C), 129.3 (CH), 128.4 (CH), 120.1 (CH), 61.8 (CH), 29.1 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{14}H_{16}N_2O_2S$, [M+Na] 299.0825, found 299.0820; Anal. Calc. for $C_{14}H_{16}N_2O_2S$: C, 60.85; H, 5.84; N, 10.14%. Found: C, 60.87; H, 5.84; N, 10.08%.

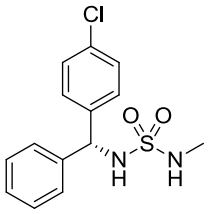
***N*-Methyl-*N*'-(4-chlorophenyl)(phenyl)methylsulfonamide (±)-4.2aac**



Prepared from **4.1aa** (198.2 mg, 1.0 mmol) using general method **Q**, purification by column chromatography (2:1 pet. ether:EtOAc) gave the product as a white solid (306.0 mg, 98%); $\mathbf{R_f}$ 0.16 (2:1 pet. ether:EtOAc); **M.p.** 126-128 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3393, 1491, 1411, 1331, 1154, 1091; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.38-7.26 (m, 9H, CH_{aryl}), 5.59 (d, J = 6.4 Hz, 1H, NHC*H*), 4.96 (d, J = 6.8 Hz, 1H, N*H*CH), 3.93 (br q, J = 4.4 Hz, 1H, N*H*CH_3), 2.47 (d, J = 4.8 Hz, 3H, NHC*H*$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 140.5 (C), 139.4 (C), 133.7 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.2 (CH), 127.3 (CH), 60.8 (CH), 29.1 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{14}H_{15}ClN_2O_2S$, [M+Na] 333.0435, found 333.0429; Anal. Calc. for $C_{14}H_{15}ClN_2O_2S$: C, 54.10; H, 4.86; N, 9.01%. Found: C, 54.09; H, 4.85; N, 8.81%; **HPLC**

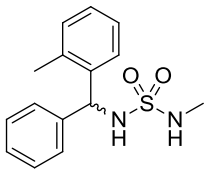
Daicel Chiralpak OD-H, 90:10 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 17.8 min, (*R*)-enantiomer t_R = 22.1 min.

_N_-Methyl-_N_'-(_R_)-(4-chlorophenyl)(phenyl)methylsulfonamide (_R_)-4.2aac



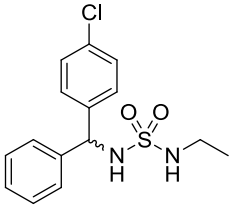
Prepared from **4.1aa** (99 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) gave the product as a white solid (101 mg, 65%). Analytical data as for **(±)-4.2aac** except; $[\alpha]_D$ = +1.8 (*c* = 1.15, $CHCl_3$, for 86% *ee* material).

_N_-Methyl-_N_'-(2-methylphenyl)(phenyl)methylsulfonamide (±)-4.2aae



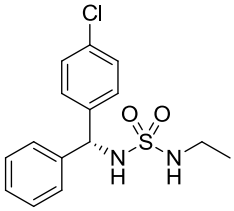
Prepared from **4.1ae** (159 mg, 0.75 mmol) using general method **P**, purified by column chromatography (2:1 pet. ether:EtOAc) to give a white solid (186 mg, 85%); $\mathbf{R_f}$ 0.38 (2:1 pet. ether:EtOAc); **M.p.** 91-93 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3393, 1408, 1328, 1153; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.44-7.41 (dd, *J* = 7.6, 1.2 Hz, 1H, CH_{aryl}), 7.35-7.16 (m, 8H, CH_{aryl}), 5.84 (d, *J* = 6.0 Hz, 1H, NHC*H*), 4.82 (br d, *J* = 6.0 Hz, 1H, N*H*CH), 3.78 (q, *J* = 5.1 Hz, 1H, N*H*CH_3), 2.49 (d, *J* = 5.6 Hz, 3H, NHC*H*$_3$), 2.30 (s, 3H, ArCH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 140.2 (C), 138.8 (C), 135.7 (C), 130.9 (CH), 128.7 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 126.6 (CH), 126.3 (CH), 58.1 (CH), 29.1 (CH_3), 19.5 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{15}H_{18}N_2O_2S$, [M+H] 313.0981, found 313.0977; Anal. Calc. for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65%. Found: C, 61.82; H, 6.25; N, 9.61%.

***N*-Ethyl-*N*'-(4-chlorophenyl)(phenyl)methylsulfonamide (±)-4.2bac**



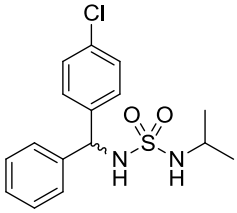
Prepared from **4.1ba** (424.5 mg, 2.0 mmol) using general method **Q**, purification by column chromatography (4:1 pet. ether:EtOAc) gave the product as a white solid (480.1 mg, 74%); $\mathbf{R_f}$ 0.23 (4:1 pet. ether:EtOAc); **M.p.** 72-75 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3385, 3012, 1491, 1417, 1329, 1153; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.38-7.26 (m, 9H, CH_{aryl}), 5.60 (d, *J* = 6.8 Hz, 1H, NHC*H*), 4.87 (d, *J* = 6.0 Hz, 1H, N*H*CH), 3.80 (t, *J* = 5.8 Hz, 1H, N*H*CH_2CH_3), 2.93-2.79 (m, 2H, NHC*H*$_2CH_3$), 0.94 (t, *J* = 7.2 Hz, 3H, CH_2CH_3); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 140.6 (C), 139.6 (C), 133.6 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.1 (CH), 127.3 (CH), 61.0 (CH), 38.0 (CH_2), 14.5 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{15}H_{17}ClN_2O_2S$, [M+Na] 347.0591, found 347.0591; Anal. Calc. for $C_{15}H_{17}ClN_2O_2S$: C, 55.46; H, 5.28; N, 8.62%. Found: C, 55.53; H, 5.31; N, 8.50%; **HPLC**: Daicel Chiralpak OD-H, 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 25.1 min, (*R*)-enantiomer t_R = 33.0 min.

***N*-Ethyl-*N*'-(*R*)-(4-chlorophenyl)(phenyl)methylsulfonamide (*R*)-4.2bac**



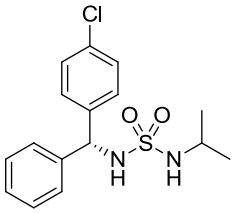
Prepared from **4.1ba** (106 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a yellow oil (81 mg, 50%). Analytical data as for **(±)-4.2bac** except; $\mathbf{[\alpha]_D}$ = +0.6 (*c* = 1.27, $CHCl_3$, for 87% *ee* material).

***N*-*iso*-Propyl-*N*'-(4-chlorophenyl)(phenyl)methylsulfonamide (±)-4.2cac**



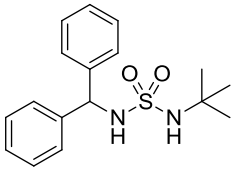
Prepared from **4.1ca** (226 mg, 1.0 mmol) using general method **Q**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (293 mg, 86%); $\mathbf{R_f}$ 0.30 (4:1 pet. ether:EtOAc); **M.p.** 142-145 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3384, 1491, 1417, 1333, 1139, 1005; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.38-7.26 (m, 9H, CH_{aryl}), 5.60 (d, *J* = 6.8 Hz, 1H, NHC*H*(Aryl)$_2$), 4.85 (d, *J* = 6.4 Hz, 1H, N*H*CH(Aryl)$_2$), 3.84 (d, *J* = 7.6 Hz, 1H, N*H*CH(CH$_3$)$_2$), 3.43-3.31 (m, 1H, NHC*H*(CH$_3$)$_2$), 1.00 (d, *J* = 6.4 Hz, 3H, CH(C$H_{3\alpha}$)(CH$_3$)), 0.97 (d, *J* = 6.4 Hz, 3H, CH(C$H_{3\beta}$)(CH$_3$)); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 140.8 (C), 139.8 (C), 133.6 (C), 128.9 (CH), 128.84 (CH), 128.79 (CH), 128.0 (CH), 127.3 (CH), 60.7 (CH), 46.2 (CH), 23.5 (CH_3), 23.4 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{16}H_{19}ClN_2O_2S$, [M+Na] 361.0748, found 361.0728; Anal. Calc. for $C_{16}H_{19}ClN_2O_2S$: C, 56.71; H, 5.65; N, 8.27%. Found: C, 56.66; H, 5.63; N, 8.24%; **HPLC**: Daicel Chiralpak OD-H, 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 26.0 min, (*R*)-enantiomer t_R = 32.1 min.

***N*-*iso*-Propyl-*N*'-(*R*)-(4-chlorophenyl)(phenyl)methylsulfonamide (*R*)-4.2cac**



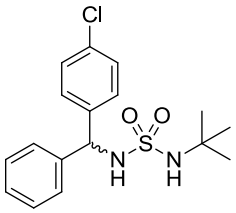
Prepared from **4.1ca** (113 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a light yellow solid (47.5 mg, 28%). Analytical data as for **(±)-4.2cac** except; $\mathbf{[\alpha]_D}$ = +1.6 (*c* = 1.04, $CHCl_3$, for 86% *ee* material).

***N*-*tert*-Butyl-*N*'-diphenylmethylsulfonamide 4.2daa**



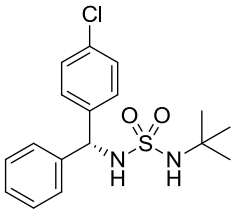
Synthesised as ***meso*-3.96** following the procedure of Borghese *et al.*,[222] using **4.30** (245 mg, 1.1 mmol) and aminodiphenylmethane (172 μL, 1.0 mmol). Work up gave a white solid (274 mg, 86%); $\mathbf{R_f}$ 0.26 (4:1 pet. ether:EtOAc); **M.p.** 140-143 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1}3383, 3011, 1391, 1321, 1144, 991; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.37-7.27 (m, 10H, CH_{aryl}), 5.63 (d, *J* = 6.4 Hz, 1H, C*H*NH), 4.78 (d, *J* = 6.4 Hz, 1H, CHN*H*), 3.85 (s, 1H, N*H*C$(CH_3)_3$), 1.17 (s, 9H, C(C*H*$_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 141.2 (C), 128.7 (CH), 127.8 (CH), 127.5 (CH), 61.7 (CH), 54.3 (C), 29.6 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{17}H_{22}N_2O_2S$, [M+Na] 341.1294, found 341.1289; Anal. Calc. for $C_{17}H_{22}N_2O_2S$: C, 64.12; H, 6.96; N, 8.80%. Found: C, 63.99; H, 6.95; N, 8.79%.

***N*-*tert*-Butyl-*N*'-(4-chlorophenyl)(phenyl)methylsulfonamide (±)-4.2dac**



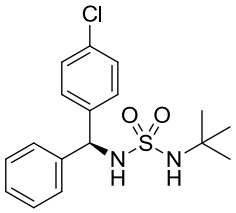
Prepared from **4.1da** (206 mg, 0.75 mmol) using general method **P**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (230 mg, 93%); $\mathbf{R_f}$ 0.29 (4:1 pet. ether:EtOAc); **M.p.** 157-159 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3383, 2980, 1491, 1324, 1145; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.36-7.26 (m, 9H, CH_{aryl}), 5.59 (d, *J* = 6.8 Hz, 1H, NHC*H*), 4.85 (d, *J* = 6.4 Hz, 1H, N*H*CH), 4.02 (s, 1H, N*H*C$(CH_3)_3$), 1.18 (s, 9H, C$(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 140.9 (C), 140.0 (C), 133.2 (C), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.8 (CH), 127.4 (CH), 60.8 (CH), 54.2 (C), 29.5 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{17}H_{21}ClN_2O_2S$, [M+Na] 375.0904, found 375.0916; Anal. Calc. for $C_{17}H_{21}ClN_2O_2S$: C, 57.86; H, 6.00; N, 7.94%. Found: C, 57.63; H, 6.02; N, 7.77%; **HPLC**: Daicel Chiralpak OD-H, 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 22.2 min, (*R*)-enantiomer t_R = 30.1 min.

***N*-*tert*-Butyl-*N*'-(*R*)-(4-chlorophenyl)(phenyl)methylsulfonamide (*R*)-4.2dac**



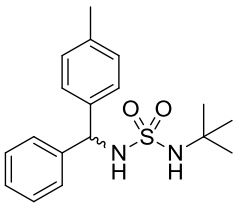
Prepared from **4.1da** (120 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (147 mg, 83%). Analytical data as for **(±)-4.2dac** except: $[\alpha]_D$ = +0.7 (*c* = 1.11, $CHCl_3$, for 86% *ee* material).

***N*-*tert*-Butyl-*N*'-(*S*)-(4-chlorophenyl)(phenyl)methylsulfonamide (*S*)-4.2dac**



Prepared from **4.1dc** (137.4 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (156.8 mg, 89%). Analytical data as for **(±)-4.2dac** except: $[\alpha]_D$ = −1.9 (*c* = 1.09, $CHCl_3$, for 81% *ee* material).

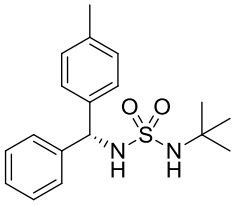
***N*-*tert*-Butyl-*N*'-(4-methylphenyl)(phenyl)methylsulfonamide (±)-4.2dad**



Prepared from **4.1dd** (127 mg, 0.5 mmol) using general method **P**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (148 mg, 89%); $\mathbf{R_f}$ 0.33 (4:1 pet. ether:EtOAc); **M.p.** 147-149 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3384, 3011, 1321, 1144, 990; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.34-7.32 (m, 4H, CH_{aryl}), 7.30-7.25 (m, 1H, CH_{aryl}), 7.22-7.20 (m, 2H, CH_{aryl}), 7.15-7.13 (m, 2H, CH_{aryl}), 5.59 (d, *J* = 6.4 Hz, 1H, NHC*H*), 4.74 (d, *J* = 6.4 Hz, 1H, N*H*CH), 3.84 (br s, 1H, N*H*C$(CH_3)_3$), 2.33 (s, 3H, ArCH_3), 1.17 (s, 9H, C$(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 141.4 (C), 138.3 (C), 137.5 (C), 129.4 (CH), 128.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 61.5 (CH), 54.3 (C), 29.6 (CH_3), 21.0 (CH_3); **HRMS** (ESI

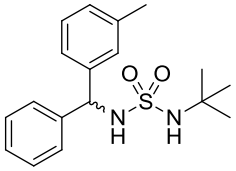
Positive) calcd. for $C_{18}H_{24}N_2O_2S$, [M+Na] 355.1451, found 355.1450; Anal. Calc. for $C_{18}H_{24}N_2O_2S$: C, 65.05; H, 7.28; N, 8.43%. Found: C, 64.98; H, 7.30; N, 8.20%; **HPLC**: Daicel Chiralpak OD-H, 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 21.1 min, (*R*)-enantiomer t_R = 26.1 min.

***N*-*tert*-Butyl-*N*'-(*R*)-(4-methylphenyl)(phenyl)methylsulfonamide (*R*)-4.2dad**



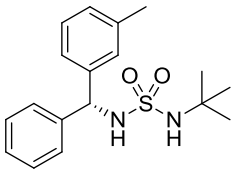
Prepared from **4.1da** (120 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a cream solid (119 mg, 71%). Analytical data as for **(±)-4.2dad** except; $[\alpha]_D$ = +3.9 (*c* = 0.99, solvent, for 95% *ee* material).

***N*-*tert*-Butyl-*N*'-(3-methylphenyl)(phenyl)methylsulfonamide (±)-4.2dah**



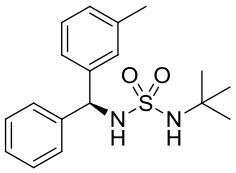
Prepared from **4.1dh** (127 mg, 0.5 mmol) using general method **P**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (155 mg, 93%); $\mathbf{R_f}$ 0.30 (4:1 pet. ether:EtOAc); **M.p.** 90-93 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3384, 2978, 1391, 1324, 1144, 990; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.34-7.19 (m, 6H, CH_{aryl}), 7.14-7.06 (m, 3H, CH_{aryl}), 5.57 (d, *J* = 6.8 Hz, 1H, C*H*NH), 4.91 (d, *J* = 6.4 Hz, 1H, CHN*H*), 4.05 (s, 1H, N*H*C$(CH_3)_3$), 2.32 (s, 3H, ArCH_3), 1.15 (s, 9H, C(C*H*$_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 141.4 (C), 141.2 (C), 138.3 (C), 128.60 (CH), 128.55 (CH), 128.4 (CH), 128.2 (CH), 127.6 (CH), 127.5 (CH), 124.5 (CH), 61.6 (CH), 54.2 (C), 29.5 (CH_3), 21.4 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{18}H_{24}N_2O_2S$, [M+Na] 355.1451, found 355.1450; Anal. Calc. for $C_{18}H_{24}N_2O_2S$: C, 65.03; H, 7.28; N, 8.43%. Found: C, 65.03; H, 7.28; N, 8.41%; **HPLC**: Daicel Chiralpak AD, 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 26.3 min, (*R*)-enantiomer t_R = 35.6 min.

***N*-*tert*-Butyl-*N*'-(*R*)-(3-methylphenyl)(phenyl)methylsulfonamide (*R*)-4.2dah**



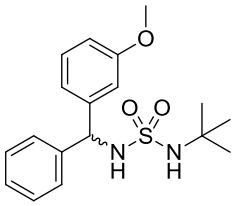
Prepared from **4.1da** (120 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (59 mg, 35%). Analytical data as for **(±)-4.2dah** except; $[\alpha]_D$ = +1.12 (*c* = 1.1, $CHCl_3$, for 76% *ee* material).

***N*-*tert*-Butyl-*N*'-(*S*)-(3-methylphenyl)(phenyl)methylsulfonamide (*S*)-4.2dah**



Prepared from **4.1da** (120 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (89 mg, 54%). Analytical data as for **(±)-4.2dah** except; $[\alpha]_D$ = −2.0 (*c* = 1.10, $CHCl_3$, for 85% *ee* material).

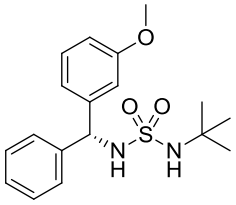
***N*-*tert*-Butyl-*N*'-(3-methoxyphenyl)(phenyl)methylsulfonamide (±)-4.2dak**



Prepared from **4.1dk** (135.2 mg, 0.5 mmol) using general method **P**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (145 mg, 83%); $\mathbf{R_f}$ 0.28 (4:1 pet. ether:EtOAc); **M.p.** 100-103 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3383, 2969, 1600, 1321, 1240, 1042; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.34-7.32 (m, 6H, CH_{aryl}), 6.92-6.88 (m, 2H, CH_{aryl}), 6.82-6.80 (m, 1H, CH_{aryl}), 5.59 (d, *J* = 6.4 Hz, 1H, NHC*H*), 4.80 (d, *J* = 6.8 Hz, 1H, N*H*CH), 3.91 (br s, 1H, N*H*C$(CH_3)_3$), 3.78 (s, 3H, OCH_3), 1.18 (s, 9H, C$(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 159.8 (C), 142.9 (C), 141.2 (C), 129.7 (CH), 128.6 (CH), 127.6 (CH), 127.5 (CH), 119.8 (CH), 113.4 (CH), 112.9 (CH), 61.6 (CH), 55.2 (CH_3), 54.2 (C), 29.5 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{18}H_{24}N_2O_3S$, [M+Na] 371.1400, found 371.1390; Anal. Calc. for

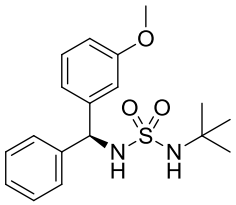
$C_{18}H_{24}N_2O_3S$: C, 62.04; H, 6.94; N, 8.04%. Found: C, 61.90; H, 6.91; N, 8.06%; **HPLC**: Daicel Chiralpak AD, 95:5 hexanes:^{i}PrOH; 0.5 mL/min; 200 nm; (*S*)-enantiomer t_R = 95.6 min, (*R*)-enantiomer t_R = 104.0 min.

***N*-*tert*-Butyl-*N*'-(*R*)-(3-methoxyphenyl)(phenyl)methylsulfonamide (*R*)-4.2dak**



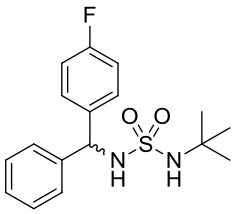
Prepared from **4.1da** (120 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (158 mg, 91%). Analytical data as for **(±)-4.2dak** except; $[\alpha]_D$ = −1.0 (*c* = 1.26, $CHCl_3$, for 97% *ee* material).

***N*-*tert*-Butyl-*N*'-(*S*)-(3-methoxyphenyl)(phenyl)methylsulfonamide (*S*)-4.2dak**



Prepared from **4.1dk** (135 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (59.3 mg, 34%). Analytical data as for **(±)-4.2dak** except: $[\alpha]_D$ = +1.1 (*c* = 1.02, $CHCl_3$, for 86% *ee* material).

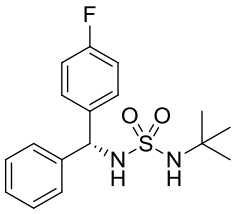
***N*-*tert*-Butyl-*N*'-(4-fluorophenyl)(phenyl)methylsulfonamide (±)-4.2dab**



Prepared from **4.1db** (129 mg, 0.5 mmol) using general method **P**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (147 mg, 87%); $\mathbf{R_f}$ 0.25 (4:1 pet. ether:EtOAc); **M.p.** 133-135 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3383, 2980, 1606, 1510, 1322, 1144, 991; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.36-7.26 (m, 7H, CH_{aryl}), 7.04-6.98 (m, 2H, CH_{aryl}),

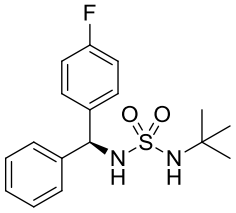
5.60 (d, J = 6.8 Hz, 1H, NHC*H*), 4.89 (d, J = 6.8 Hz, 1H, N*H*CH), 4.05 (s, 1H, N*H*C$(CH_3)_3$), 1.17 (s, 9H, C(C*H*$_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 162.1 (C, d, $^1J_{CF}$ = 246 Hz), 141.1 (C), 137.1 (C, d, $^4J_{CF}$ = 2.9 Hz), 129.2 (CH, d, $^3J_{CF}$ = 8.8 Hz), 128.8 (CH), 127.9 (CH), 127.4 (CH), 115.5 (CH, d, $^2J_{CF}$ = 20.3 Hz), 61.0 (CH), 54.4 (C), 29.5 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −114.1; **HRMS** (ESI Positive) calcd. for $C_{17}H_{21}FN_2O_2S$, [M+Na] 359.1200, found 359.1197; Anal. Calc. for $C_{17}H_{21}FN_2O_2S$: C, 60.69; H, 6.29; N, 8.33%. Found: C, 60.58; H, 6.26; N, 8.22%; **HPLC**: Daicel Chiralpak OD-H, 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 20.1 min, (*R*)-enantiomer t_R = 25.2 min.

***N*-*tert*-Butyl-*N*'-(*R*)-(4-fluorophenyl)(phenyl)methylsulfonamide (*R*)-4.2dab**



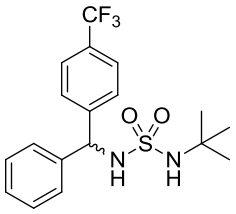
Prepared from **4.1da** (120 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (151 mg, 90%). Analytical data as for **(±)-4.2dab** except: **$[\alpha]_D$** = +0.5 (*c* = 0.97, $CHCl_3$, for 95% *ee* material).

***N*-*tert*-Butyl-*N*'-(*S*)-(4-fluorophenyl)(phenyl)methylsulfonamide (*S*)-4.2dab**



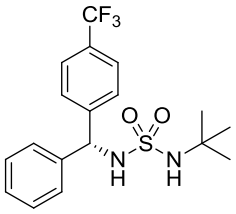
Prepared from **4.1db** (129.2 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (69 mg, 41%). Analytical data as for **(±)-4.2dab** except: **$[\alpha]_D$** = −1.0 (*c* = 1.04, $CHCl_3$, for 80% *ee* material).

***N*-*tert*-Butyl-*N*'-(4-trifluoromethylphenyl)(phenyl)methylsulfonamide (±)-4.2dal**



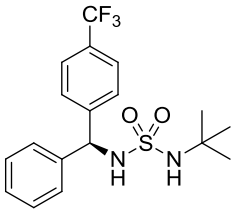
Prepared from **4.1dl** (154 g, 0.5 mmol) using general method **P**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (167 mg, 87%); $\mathbf{R_f}$ 0.13 (4:1 pet. ether:EtOAc); **M.p.** 140-143 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3382, 2979, 1421, 1326, 1169, 1144, 991; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.60 (d, J = 8.0 Hz, 2H, CH_{aryl}), 7.49 (d, J = 8.8 Hz, 2H, CH_{aryl}), 7.40-7.28 (m, 5H, CH_{aryl}), 5.67 (d, J = 6.4 Hz, 1H, C*H*NH), 4.83 (d, J = 6.8 Hz, 1H, CHN*H*), 3.98 (s, 1H. N*H*C$(CH_3)_3$), 1.19 (s, 9H, C(CH_3)$_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 145.3 (C), 140.6 (C), 129.8 (C, q, $^2J_{CF}$ = 32 Hz), 128.9 (CH), 128.2 (CH), 127.8 (CH), 127.5 (CH), 125.5 (CH, q, $^3J_{CF}$ = 3.6 Hz), 124.0 (C, q, $^1J_{CF}$ = 271 Hz), 61.2 (CH), 54.4 (C), 29.5 (CH_3); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ_F −62.5; **HRMS** (ESI Positive) calcd. for $C_{18}H_{21}F_3N_2O_2S$, [M+Na] 409.1168, found 409.1167; Anal. Calc. for $C_{18}H_{21}F_3N_2O_2S$: C, 55.95; H, 5.48; N, 7.25%. Found: C, 55.95; H, 5.47; N, 7.12%; **HPLC**: Daicel Chiralpak OD-H, 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 13.6 min, (*R*)-enantiomer t_R = 22.1 min.

***N*-*tert*-Butyl-*N*'-(*R*)-(4-trifluoromethylphenyl)(phenyl)methylsulfonamide (*R*)-4.2dal**



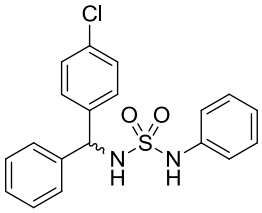
Prepared from **4.1da** (120 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (162 mg, 84%). Analytical data as for **(±)-4.2dal** except: $\mathbf{[\alpha]_D}$ = −3.7 (*c* = 1.35, $CHCl_3$, for 98% *ee* material).

***N*-*tert*-Butyl-*N*'-(*S*)-(4-trifluoromethylphenyl)(phenyl)methylsulfonamide (*S*)-4.2dal**



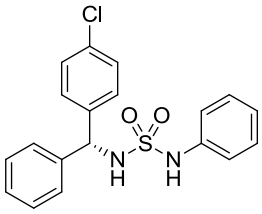
Prepared from **4.1dl** (154 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a white solid (137 mg, 71%). Analytical data as for **(±)-4.2dal** except: $[\alpha]_D$ = +2.7 (*c* = 1.43, $CHCl_3$, for 78% *ee* material).

***N*-Phenyl-*N*'-(4-chloromethylphenyl)(phenyl)methylsulfonamide (±)-4.2eac**



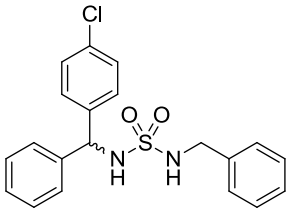
Prepared from **4.1ea** (260 mg, 1.0 mmol) using general method **Q**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a colourless oil (360 mg, 96%); $\mathbf{R_f}$ 0.24 (4:1 pet. ether:EtOAc); **M.p.** 131-133 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3388, 1602, 1495, 1155, 954; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.21-7.12 (m, 7H, CH_{aryl}), 7.08-7.03 (m, 5H, CH_{aryl}), 6.89-6.86 (m, 2H, CH_{aryl}), 6.82 (br s, 1H, NHPh), 5.57 (d, *J* = 7.6 Hz, 1H, C*H*NH), 5.39 (d, *J* = 6.8 Hz, 1H, CHN*H*); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 139.8 (C), 138.7 (C), 136.7 (C), 133.5 (C), 129.2 (CH), 128.71 (CH), 128.67 (CH), 128.6 (CH), 127.9 (CH), 127.2 (CH), 124.1 (CH), 119.1 (CH), 60.9 (CH); **HRMS** (ESI Positive) calcd. for $C_{19}H_{17}ClN_2O_2S$, [M+Na] 395.0591, found 395.0599; Anal. Calc. for $C_{19}H_{17}ClN_2O_2S$: C, 61.20; H, 4.60; N, 7.51%. Found: C, 61.21; H, 4.54; N, 7.43%; **HPLC**: Daicel Chiralpak OD-H, 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 29.6 min, (*R*)-enantiomer t_R = 35.6 min.

***N*-Phenyl-*N*'-(*R*)-(4-chloromethylphenyl)(phenyl)methylsulfonamide (*R*)-4.2eac**



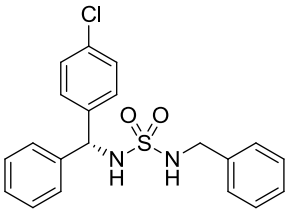
Prepared from **4.1ea** (130 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a colourless oil (120 mg, 64%). Analytical data as for **(±)-4.2eac** except: $[\alpha]_D = -3.3$ (*c* = 1.15, $CHCl_3$, for 90% *ee* material).

***N*-Benzyl-*N*'-(4-chloromethylphenyl)(phenyl)methylsulfonamide (±)-4.2fac**



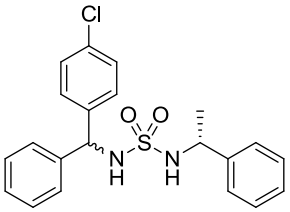
Prepared from **4.1fa** (110 mg, 0.4 mmol) using general method **P**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a cream solid (155 mg, 100%). $\mathbf{R_f}$ 0.24 (4:1 pet. ether:EtOAc); **M.p.** 133-135 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3380, 1492, 1418, 1336, 1153; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.38-7.26 (m, 12H, CH_{aryl}), 7.04-7.02 (m, 2H, CH_{aryl}), 5.64 (d, *J* = 6.4 Hz, 1H, NHC*H*), 4.90 (d, *J* = 6.4 Hz, 1H, N*H*CH), 4.13 (t, *J* = 5.8 Hz, 1H, N*H*CH_2), 4.02-3.93 (m, 2H, NHCH_2); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 140.5 (C), 139.4 (C), 135.9 (C), 133.8 (C), 129.0 (CH), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.3 (CH), 60.9 (CH), 47.3 (CH_2); **HRMS** (ESI Positive) calcd. for $C_{20}H_{19}ClN_2O_2S$, [M+Na] 409.0748, found 409.0747; Anal. Calc. for $C_{20}H_{19}ClN_2O_2S$: C, 62.09; H, 4.95; N, 7.24%. Found: C, 62.07; H, 4.95; N, 6.86%; **HPLC** Daicel Chiralpak OD-H, 95:5 hexanes:^{i}PrOH; 1.0 mL/min; 200 nm; (*S*)-enantiomer t_R = 21.5 min, (*R*)-enantiomer t_R = 32.9 min.

***N*-Benzyl-*N*'-(*R*)-(4-chloromethylphenyl)(phenyl)methylsulfonamide (*R*)-4.2fac**



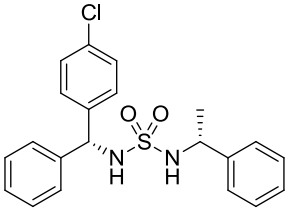
Prepared from **4.1fa** (137.2 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a cream solid (118 mg, 61%). Analytical data as for **(±)-4.2fac** except: $[\alpha]_D$ = +3.4 (*c* = 1.10, $CHCl_3$, for 88% *ee* material).

***N*-(*R*)-(1-phenylethyl)-*N*'-(4-chloromethylphenyl)(phenyl)methylsulfonamide (*R*,±)-4.2gac**



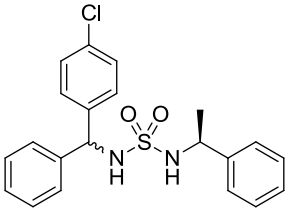
Prepared from **(*R*)-4.1ga** (288.4 mg, 1.0 mmol) using general method **Q**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a colourless oil (351.9 mg, 88%); $\mathbf{R_f}$ 0.27 (4:1 pet. ether:EtOAc); $[\alpha]_D$ = +8.1 (*c* = 0.91, $CHCl_3$); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3383, 1492, 1419, 1330, 1155, 1091, 968; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 1:1 mixture of α-diastereoisomer and β-diastereoisomer 7.33-7.05 (m, 28H, $CH_{(\alpha+\beta)aryl}$), 5.49 (app t, *J* = 7.0 Hz, 2H, NHC$H_{\alpha+\beta}(Ar)_2$), 4.97 (d, *J* = 6.8 Hz, 1H, NH_αCH$(Ar)_2$), 4.88 (d, *J* = 6.8 Hz, 1H, NH_βCH$(Ar)_2$), 4.62 (d, *J* = 6.4 Hz, 1H, NH_αCHMePh), 4.50 (d, *J* = 6.8 Hz, 1H, NH_βCHMePh), 4.43-4.35 (m, 2H, NHC$H_{\alpha+\beta}$MePh), 1.33 (d, *J* = 7.2 Hz, 3H, $CH_{3\beta}$), 1.30 (d, *J* = 6.8 Hz, 3H, $CH_{3\alpha}$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C α-diastereoisomer: 142.6 (C), 140.8 (C), 139.5 (C), 133.4 (C), 128.83 (CH), 128.75 (CH), 128.70 (CH), 128.6 (CH), 127.92 (CH), 127.62 (CH), 127.16 (CH), 125.9 (CH), 60.7 (CH), 53.8 (CH), 23.7 (CH_3); β-diastereoisomer: 142.5 (C), 140.6 (C), 139.8 (C), 133.5 (C), 128.83 (CH), 128.75 (CH), 128.68 (CH), 128.6 (CH), 127.89 (CH), 127.59 (CH), 127.21 (CH), 126.0 (CH), 60.8 (CH), 53.9 (CH), 23.6 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{21}H_{21}ClN_2O_2S$, [M+Na] 423.0904, found 423.0915.

***N*-(*R*)-(1-phenylethyl)-*N*'-(*R*)-(4-chloromethylphenyl)(phenyl)methylsulfonamide (*R*,*R*)-4.2gac**



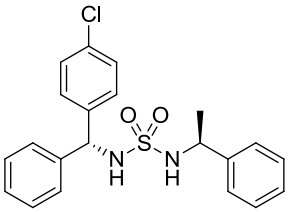
Prepared from **(*R*)-4.1ga** (144.2 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a colourless oil (116.5 mg, 58%). Analytical data as for **(*R*,±)-4.2gac** (α-diastereoisomer) except: $[\alpha]_D$ = +7.8 (*c* = 1.12, $CHCl_3$, for 83% *ee* material measured on acetamide).

***N*-(*S*)-(1-phenylethyl)-*N*'-(4-chloromethylphenyl)(phenyl)methylsulfonamide (*S*,±)-4.2gac**



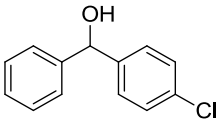
Prepared from **(*S*)-4.1ga** (288.4 mg, 1.0 mmol) using general method **Q**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a colourless oil (146.1 mg, 36%). Analytical data as for **(*R*,±)-4.2gac** except: $[\alpha]_D$ = −8.0 (*c* = 0.90, $CHCl_3$); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3383, 1492, 1420, 1330, 1155, 968.

***N*-(*S*)-(1-phenylethyl)-*N*'-(*R*)-(4-chloromethylphenyl)(phenyl)methylsulfonamide (*S*,*R*)-4.2gac**



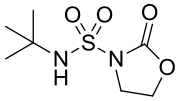
Prepared from **(*S*)-4.1ga** (144.2 mg, 0.5 mmol) using general method **R**, purified by column chromatography (4:1 pet. ether:EtOAc) to give a colourless oil (146.1 mg, 36%). Analytical data as for **(*R*,±)-4.2gac** (β-diastereoisomer) except: $[\alpha]_D$ = −5.5 (*c* = 1.07, $CHCl_3$, for 85% *ee* material measured on acetamide).

(4-Chlorophenyl)(phenyl)methanol 3.117c[320]



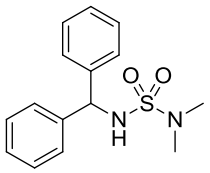
A flame-dried Schlenk was charged with 4-chlorobenzaldehyde (141 mg, 1.0 mmol) was THF (10 mL) and cooled to 0 °C. Phenylmagnesium bromide (2.0 M in THF, 1 mL, 2.0 mmol) was added dropwise with stirring. The solution was stirred overnight and allowed to warm to rt. The reaction mixture was then quenched with sat. NH_4Cl solution (20 mL), extracted with Et_2O (2 × 20 mL), the organics were dried (Na_2SO_4) and concentrated to a colourless oil. This was purified by column chromatography (9:1 pet. ether:EtOAc) to afford the product as a colourless oil (162 mg, 74%). $\mathbf{R_f}$ 0.09 (9:1 pet. ether:EtOAc); **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3603, 3011, 1490, 1090, 1014; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.34-7.25 (m, 9H, CH_{aryl}), 5.80 (d, *J* = 3.6 Hz, 1H, C*H*OH), 2.25 (d, *J* = 3.6 Hz, 1H, CHO*H*); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 143.3 (C), 142.1 (C), 133.1 (C), 128.52 (CH), 128.47 (CH), 127.8 (CH), 127.7 (CH), 126.4 (CH), 75.4 (CH); **HRMS** (EI) calcd. for $C_{13}H_{11}ClO$, $[M^+]$ 218.0493, found 218.0488; **HPLC**: Daicel Chiralpak AD, 95:5 hexanes:^{i}PrOH; 0.5 mL/min; 200 nm; (*R*)-enantiomer t_R = 36.0 min, (*S*)-enantiomer t_R = 39.6 min. These data were consistent with literature values.[320]

***N*-(*tert*-Butyl)-2-oxo-1,3-oxazolidine-3-sulfonamide 4.30**



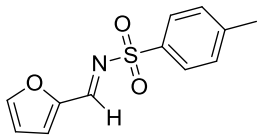
Synthesised as **(*R*)-3.98** following the procedure of Borghese *et al.*,[222] using *tert*-butylamine (578 µL, 5.5 mmol) to give the product as a white solid (896 mg, 81%); **M.p.** 134-137 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3545, 3366, 2982, 1772, 1392, 1361, 1167; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 5.52 (br s, 1H, N*H*C$(CH_3)_3$), 4.44-4.40 (m, 2H, NCH_2CH_2O), 4.08-4.04 (m, 2H, NCH_2CH_2O), 1.37 (s, 9H, C$(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 153.4 (C), 62.4 (CH_2), 55.6 (C), 44.5 (CH_2), 29.4 (CH_3); **HRMS** (ESI Positive) calcd. for $C_7H_{14}N_2O_4S$, [M+Na] 245.0566, found 245.0574; Anal. Calc. for $C_7H_{14}N_2O_4S$: C, 37.83; H, 6.36; N, 12.60%. Found: C, 37.69; H, 6.27; N, 12.46%. These data were consistent with literature values.[321]

***N,N*-Dimethyl-*N*'-diphenylmethylsulfonamide 3.123**



Synthesised as ***meso*-3.96** following the procedure of Borghese *et al.*,[222] using **3.119a** (160 mg, 0.48 mmol), dimethylamine hydrochloride (36 mg, 0.44 mmol) and triethylamine (304 μL, 2.19 mmol). Work up gave a colourless oil which was purified using column chromatography (4:1 pet. ether:EtOAc) to give the product as a white solid (83.0 mg, 59%); $\mathbf{R_f}$ 0.15 (4:1 pet. ether:EtOAc); **M.p.** 111-114 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3390, 3011, 1454, 1331, 1148, 961; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.35-7.23 (m, 10H, CH_{aryl}), 5.61 (d, *J* = 6.8 Hz, 1H, C*H*NH), 5.18 (d, *J* = 7.2 Hz, 1H, CHN*H*), 2.53 (s, 6H, N(CH_3)$_2$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 141.3 (C), 128.6 (CH), 127.6 (CH), 127.3 (CH), 61.5 (CH), 36.5 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{15}H_{18}N_2O_2S$, [M+Na] 313.0981, found 313.0979; Anal. Calc. for $C_{15}H_{18}N_2O_2S$: C, 62.04; H, 6.25; N, 9.65%. Found: C, 61.89; H, 6.23; N, 9.61%.

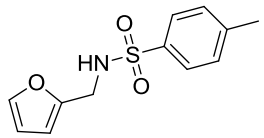
***N*-(Furan-2-ylmethylene)-4-methylbenzenesulfonamide 5.28**[322]



A suspension of *p*-toluenesulfonamide (3.42 g, 20 mmol), 2-furaldehyde (1.66 mL, 20mmol) in tetraethoxysilane (4.9 mL) was stirred a 160 °C for 4 h in a flask fitted with a short distillation kit. Allowed to cool, then diluted with Et_2O (20 mL). The resulting brown solid was collected by filtration, washed with cold Et_2O (20 mL) and recrystallised from EtOAc/hexanes to afford the product as a brown crystalline solid (2.37 g, 47%); $\mathbf{R_f}$ 0.51 (1:1 hexanes:EtOAc); **M.p.** 99-101 °C (EtOAc/hexanes); lit. 100.7-102.8 °C;[322] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 1607, 1466, 1323, 1161, 1090, 823; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 8.80 (s, 1H, N=CH), 7.87 (d, *J* = 8.4 Hz, 2H, CH_{aryl}), 7.73 (m, 1H, CH_{aryl}), 7.34-7.31 (m, 3H, CH_{aryl}), 6.63 (dd, *J* = 3.6, 1.7 Hz, 1H, CH_{aryl}), 2.42 (s, 3H, $ArCH_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 155.6 (CH), 149.7 (CH), 149.0 (C), 144.5 (C), 135.1 (C), 129.7 (CH), 128.0 (CH), 124.6 (CH), 113.7 (CH), 21.6 (CH_3);

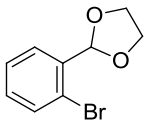
HRMS (ESI Positive) calcd. for $C_{12}H_{11}NO_3S$, [M+Na] 272.0352, found 272.0348; These data were consistent with literature values.[322]

***N*-(Furan-2-ylmethyl)-4-methylbenzenesulfonamide 5.30**



Sodium borohydride (112 mg, 3 mmol) was added to a suspension of **5.28** (249 mg, 1 mmol) in methanol (25 mL) at 0 °C. The suspension was stirred at rt for 16 h then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (20 mL) and 2 M HCl (2 × 20 mL). The organics were washed with H_2O (20 mL), dried (Na_2SO_4) and concentrated to a cream solid (203 mg, 81%); $\mathbf{R_f}$ 0.60 (1:1 pet. ether:EtOAc); **M.p.** 112-114 °C; lit. 111-112 °C;[323] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3387, 1410, 1334, 1161, 1119; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.72 (dt, *J* = 8.3, 1.9 Hz, 2H, CH_{aryl}), 7.30-7.27 (m, 2H, CH_{aryl}), 7.25 (dd, *J* = 1.9, 0.8 Hz, 1H, CH_{aryl}), 6.22 (dd, *J* = 3.2, 1.9 Hz, 1H, CH_{aryl}), 6.10-6.09 (m, 1H, CH_{aryl}), 4.82 (t, J = 5.8 Hz, 1H, N*H*CH_2), 4.18 (d, *J* = 6.0 Hz, 2H, NHC*H*$_2$), 2.42 (s, 3H, CH_3);**^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 149.5 (C), 143.5 (C), 142.5 (CH), 136.8 (C), 129.6 (CH), 127.1 (CH), 110.4 (CH), 108.2 (CH), 40.1 (CH_2), 21.5 (CH_3); **HRMS** (ESI Positive) calcd. for $C_{12}H_{13}NO_3S$, [M+Na] 274.0508, found 274.0507; These data were consistent with literature values.[324]

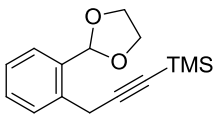
2-(2-Bromophenyl)-1,3-dioxolane 5.39[325]



A suspension of 2-bromobenzaldehyde (11.7 mL, 0.1 mol), ethylene glycol (6.7 mL, 0.12 mol) and *p*-toluenesulfonic acid monohydrate (190 mg, 1 mmol) in toluene (60 mL) was stirred at reflux with a Dean-Stark trap overnight. The reaction mixture was allowed to cool, and then poured into a stirred sat. $NaHCO_3$ solution (150 mL). This was then extracted with MTBE (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), concentrated to a yellow oil and purified by distillation under reduced pressure (102-104 °C, 0.69-0.71 mmHg) to give a light yellow oil (19.6 g, 86%). $\mathbf{R_f}$ 0.55 (1:1 pet. ether:EtOAc); **B.p.** 102-104 °C, 0.69-0.71 mmHg;

lit. 98 °C, 0.1 mmHg;[325] **IR** (liquid film) ν_{max}/cm^{-1} 3424, 2955, 2888, 1697, 1389, 1211, 1091, 757; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.60 (dd, *J* = 8.0, 1.6 Hz, 1H, CH_{aryl}), 7.56 (dd, *J* = 8.0, 1.2 Hz, 1H, CH_{aryl}), 7.33 (app. t, *J* = 7.6 Hz, 1H, CH_{aryl}), 7.21 (td, *J* = 7.6, 1.6 Hz, 1H, CH_{aryl}), 6.10 (s, 1H, OCHO), 4.19-4.03 (m, 4H, -O$(CH_2)_2$O-); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 136.5 (C), 132.8 (CH), 130.5 (CH), 127.7 (CH), 127.3 (CH), 122.8 (C), 102.5 (CH), 65.3 (CH_2); **HRMS** (EI) calcd. for $C_9H_9BrO_2$, [M^+] 227.9780, found 227.9789. This data was consistent with literature values.[325]

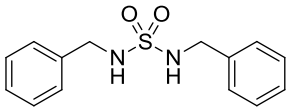
(3-(2-(1,3-Dioxolan-2-yl)phenyl)prop-1-yn-1-yl)trimethylsilane 5.40[326]



Prepared according to the procedure of Knobloch *et al.*[326] an oven dried flask was charged with 2-(2-bromophenyl)-1,3-dioxolane **5.39** (8.25 g, 36 mmol) and THF (200 mL) and cooled to –60 °C. *n*-Butyllithium (2.5 M in hexanes, 17.3 mL, 43.2 mmol) was added dropwise, and the solution was stirred at –60 °C for 2 h, became a light orange suspension. Magnesium bromide (7.29 g, 39.6 mmol) was suspended in Et_2O (40 mL) and stirred vigorously at rt for 1.5 h, the resulting biphasic mixture was added dropwise to the reaction mixture at –55 °C. The reaction mixture was stirred at rt for 1.5 h. 3-Bromo-1-propynyltrimethylsilane (7.06 mL, 43.2 mmol) was added and stirred at reflux for 2 h. The yellow solution was allowed to cool and poured into a 1:1 mixture of sat. NH_4Cl solution and H_2O (200 mL) with stirring. The mixture was separated and the aqueous layer washed with MTBE (100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to a yellow oil which was then purified by column chromatography (9:1 hexanes:EtOAc) to afford the product as a yellow oil (7.16 g, 76%). **R_f** 0.34 (9:1 pet. ether:EtOAc); **IR** (Liquid film) ν_{max}/cm^{-1}3417, 2959, 2891, 2176, 1251, 1077, 844, 759; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 7.59-7.57 (m, 1H, CH_{aryl}), 7.53 (dd, *J* = 7.4, 1.4 Hz, 1H, CH_{aryl}), 7.36 (td, *J* = 7.4, 1.5 Hz, 1H, CH_{aryl}), 7.27-7.24 (m, 1H, CH_{aryl}), 5.98 (s, 1H, -OCHO-), 4.13-4.01 (m, 4H, -O$(CH_2)_2$O-), 3.82 (s, 2H, $CH_2C{\equiv}C$), 0.18 (s, 9H, $Si(CH_3)_3$); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 134.9 (C), 134.6 (C), 129.3 (CH), 128.8 (CH), 126.6 (CH), 126.2 (CH), 103.9 (C), 101.9 (CH), 87.3 (C), 65.1 (CH_2), 23.1 (CH_2) 0.05 (CH_3); **HRMS** (ESI

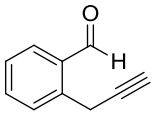
Positive) calcd. for $C_{15}H_{20}O_2Si$, [M+Na] 283.1125, found 283.1120. This compound is reported in the literature but no analytical data are quoted.[326]

***N,N'*-Dibenzylsulfamide 5.31**[327]



Sodium borohydride (56.1 mg, 1.5 mmol) was added to a stirred solution of **4.1fa** (137.2 mg, 0.5 mmol) in MeOH (25 mL) at 0 °C. The solution was stirred for 6 h and allowed to warm to rt. The colourless solution was concentrated to a white solid, this was taken up in CH_2Cl_2 (25 mL) and washed with 1 M HCl (2 × 25 mL). The organics were washed with H_2O (20 mL), dried ($MgSO_4$) and concentrated to a white solid (123 mg, 89%); $\mathbf{R_f}$ 0.54 (2:1 pet. ether:EtOAc); **M.p.** 177-180 °C; lit. 181-183 °C;[327] **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3381, 3271, 1455, 1415, 1327, 1151; **^{1}H NMR** (400.1 MHz, DMSO-d_6) δ_H 7.45 (t, J = 6.4 Hz, 2H, N*H*CH_2), 7.33-7.32 (m, 8H, CH_{aryl}), 7.29-7.23 (m, 2H, CH_{aryl}), 4.02 (d, J = 6.4 Hz, 4H, NHC*H*$_2$); **^{13}C NMR** (100.6 MHz, DMSO-d_6) δ_C 138.4 (C), 128.2 (CH), 127.7 (CH), 127.0 (CH), 45.9 (CH_2); **HRMS** (ESI Positive) calcd. for $C_{14}H_{16}N_2O_2S$, [M+Na] 299.0825, found 299.0815. These data were consistent with literature values.[327]

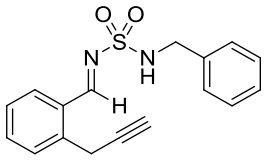
2-(Prop-2-yn-1-yl)benzaldehyde 5.41



A solution of (3-(2-(1,3-dioxolan-2-yl)phenyl)prop-1-yn-1-yl)trimethylsilane **5.40** (2.0 g, 7.68 mmol) and K_2CO_3 (53.1 mg, 0.38 mmol) in MeOH (50 mL) was stirred at reflux for 90 min. The reaction mixture was diluted with H_2O (50 mL) and washed with EtOAc (2 × 50 mL). The organics were dried ($MgSO_4$) and concentrated to a yellow oil (1.35 g). The oil was taken up in acetone (24 mL) and H_2O (20 mL) and *p*-toluenesulfonic acid monohydrate (68.2 mg, 0.36 mmol) was added. The solution was stirred at reflux for 45 min. The resulting yellow solution was poured into sat. $NaHCO_3$ solution (100 mL) and extracted with MTBE (2 × 50 mL). The organics were dried ($MgSO_4$) and concentrated to a yellow oil. Purified by column chromatography (19:1 hexanes:EtOAc) to give a light yellow oil (737 mg, 72%). $\mathbf{R_f}$ 0.40 (4:1

hexanes:EtOAc); **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 10.20 (s, 1H, CHO), 7.81 (dd, *J* = 7.6, 1,2 Hz, 1H, CH_{aryl}), 7.74 (d, *J* = 7.6 Hz, 1H, CH_{aryl}), 7.59 (td, *J* = 7.5, 1.3 Hz, 1H, CH_{aryl}), 7.45 (t, *J* = 7.4 Hz, 1H, CH_{aryl}), 4.08 (d, *J* = 2.8 Hz, 2H, CH_2), 2.26 (t, *J* = 2.8 Hz, 1H, C≡CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 192.8 (CH), 137.8 (C), 134.0 (CH), 133.9 (CH), 133.1 (C), 129.8 (CH), 127.3 (CH), 81.1 (C), 71.7 (CH), 22.6 (CH_2). These data were consistent with literature values.[328]

***N*-benzyl-*N*'-[2-(prop-2-yn-1-yl)phenylmethylidene]sulfamide 5.42**



Prepared from *N*-benzylsulfamide **4.4f** (373 mg, 2.0 mmol) and **5.41** (317 mg, 2.2 mmol) using general method **K** refluxed for 2.5 h, work up gave a yellow oil which was purified using column chromatography (4:1 hexanes:EtOAc) to give the product as a white solid (445 mg, 65%); **R_f** 0.13 (4:1 hexanes:EtOAc); **M.p.** 99-100 °C; **IR** ($CHCl_3$) ν_{max}/cm^{-1} 3377, 3307, 1611, 1593, 1570, 1414, 1382, 1158; **^{1}H NMR** (400.1 MHz, $CDCl_3$) δ_H 9.16 (s, 1H, N=CH), 7.92 (dd, *J* = 7.8, 1.4 Hz, 1H, CH_{aryl}), 7.66 (br d, *J* = 7.2 Hz, 1H, CH_{aryl}), 7.59 (td, *J* = 7.5, 1.5 Hz, 1H, CH_{aryl}), 7.42 (br t, *J* = 7.6 Hz, 1H, CH_{aryl}), 7.36-7.24 (m, 5H, CH_{aryl}), 4.76 (t, *J* = 6.0 Hz, 1H, N*H*CH_2), 4.36 (d, *J* = 6.4 Hz, 2H, NHC*H*$_2$), 3.92 (d, *J* = 2.8 Hz, 2H, C*H*$_2$C≡CH), 2.52 (t, *J* = 2.6 Hz, 1H, C≡CH); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ_C 168.1 (CH), 139.1 (C), 136.1 (C), 134.2 (CH), 132.1 (CH), 130.0 (CH), 129.6 (C), 128.6 (CH), 128.0 (CH), 127.8 (CH), 127.5 (CH), 80.8 (C), 72.1 (CH), 47.7 (CH_2), 23.1 (CH_2); **HRMS** (ESI Positive) calcd. for $C_{17}H_{16}N_2O_2S$, [M+H] 335.0826, found 335.0825; Anal. Calc. for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97%. Found: C, 65.06; H, 5.18; N, 8.97%.

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